EXHIBIT F

I. BACKGROUND

1. My name is Cheryl D. Blume, Ph.D. I am the President of Pharmaceutical Development Group, Inc. (hereinafter, "PDG") a consulting firm specializing in pharmaceutical development and registration activities, located in Tampa, Florida. As described in the Curriculum Vitae attached as Exhibit 1, my background includes holding several executive positions in pharmaceutical companies over a period of 20 years, including Vice President of Scientific Affairs for Mylan Laboratories, Inc., and Executive Vice President and Chief Operations Officer for Somerset Pharmaceuticals, Inc. I also was a member of the Board of Directors of Somerset.
2. I was responsible for overseeing preclinical and clinical (Phases I-IV) programs associated with pharmaceutical product development and the securing of premarketing approvals for over 100 new prescription pharmaceutical drugs from the U.S., Food and Drug Administration (FDA). These products included both new (brand name) and generic drug products. These responsibilities included the design, execution and interpretation of pivotal preclinical and clinical trials.
3. My duties included direction of all phases of interactions with the FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Application (ANDAs) Supplements to New Drug Applications (sNDAs), drafting labeling and other aspects of the approval procedures. I have been centrally involved in supervising the collection and evaluation of post marketing adverse medical events, the design and implementation of studies to assess post-marketing signals, and the preparation and dissemination of updated product information to health providers and patients.
4. I have been asked by counsel to provide an opinion on whether Neurontin contributes to mood and behavior disturbances including self-injurious actions and suicide. I have also been asked to evaluate the actions taken by defendants (Warner Lambert Co., Parke-Davis and Pfizer; hereinafter "Pfizer Defendants") with respect to the regulatory and marketing efforts associated with Neurontin (gabapentin). The scientific opinions set forth in this report are true to a reasonable degree of scientific certainty based on the data and information provided to date.
5. I reserve the right to supplement this report if additional information is provided. I cannot possibly list all of the documentation that supports my opinions; however, I have based my opinions in part upon my education, personal experience, and review of documents disclosed during the pendency of this litigation, included but not limited to sources containing adverse events associated with Neurontin, Pfizer Defendants' internal Research Reports, Investigational and New Drug Applications, Annual Reports, adverse event surveillance databases (Pfizer's internal database, Spontaneous Reporting System (SRS), Adverse Event Reporting System (AERS), and the World Health Organization (WHO)), Periodic Safety Update Reports, FDA records, international regulatory efforts, expert reports prepared by Drs. Trimble, Kruszewski and Roth, medical literature, deposition transcripts and exhibits.

II. INTRODUCTION

6. The documentary evidence in this case demonstrates that the Pfizer Defendants were aware of multiple pre-marketing clinical trial reports and post-marketing patient events of self-injurious behavior, including suicide, in association with Neurontin.

7. Multiple avenues of neuropharmacologic research have supported the biologic plausibility of Neurontin-precipitated self-injurious behavior for several years.

8. Despite the fact that Neurontin is approved for two relatively small patient populations (adjunctive treatment of epilepsy and pain associated with post herpetic neuralgia), Pfizer Defendants aggressively and illegally promoted Neurontin for multiple off-label uses including (but not limited to) treatment of bipolar disorders, neuropathic pain, drug and alcohol withdrawal syndromes, amyotrophic lateral sclerosis, migraine, restless legs syndrome, monotherapy and other psychiatric and non-psychiatric conditions.[1] As a result, sales quickly skyrocketed and Neurontin became a leading US drug product.[2] These sales were accomplished using Pfizer Defendants' marketing plan to extend Neurontin uses to a wide variety of off-label (unapproved) indications.

9. These indications included patient populations particularly vulnerable to Neurontin-related self-injurious behaviors (patients with psychiatric disorders, pain-related disorders, drug and alcohol withdrawal-related events and others).

10. The Pfizer Defendants, failed to respond to accumulating safety signals related to self-injurious events and did not appropriately warn physicians of the various at-risk populations receiving Neurontin. As such, vulnerable patients received Neurontin for unapproved uses without the benefit of corroborating clinical trial data and were simultaneously not warned of the drug's potential for eliciting psychobiological adverse events and self-injurious behavior.

11. Pfizer Defendants, as the innovator, NDA sponsor and marketer of Neurontin, were responsible for the conduct of epidemiologic and clinical studies designed to assess the potential for causing self-injurious behaviors in all marketed patient populations.

12. Pfizer Defendants had a duty to warn prescribers and patients of these adverse events. Unfortunately, relevant updates to the Neurontin label relating to suicide attempts and suicide did not occur until December 2005 and even then did not adequately reflect the totality of the postmarketing experiences.

13. Despite the growing off-label use of Neurontin, Pfizer Defendants did not secure FDA approval for any of these indications. In fact, in many cases Pfizer Defendants actually decided to not evaluate Neurontin's efficacy in treating these off-label indications in controlled clinical trials.[3] Even more concerning are the few instances in which clinical trials were performed and Neurontin failed to show any benefit compared to placebo[4] or comparator drugs[5]. Notwithstanding these failures to demonstrate efficacy, Pfizer Defendant's continued to market Neurontin for these off-label uses.

14. Off label uses of Neurontin encompassed the majority of the drug's revenues, with some estimates as high as 90% of Neurontin prescriptions.[6] This was brought to light in July 1996

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[1] See www.usdoj.gov/opa/pr/2004/May04_civ_322.htm. "This illegal and fraudulent promotion scheme corrupted the information process relied upon by doctors in their medical decision making, thereby putting patients at risk." *Ibid.*

[2] J Schmit, USA Today, August 16, 2004; Pfizer, Inc.; January 24, 2001

[3] *See* documents V048094, V054306. *See also* Pfizer_LTive_0008792 at 0008800, which reflects Defendants' CI-945 Clinical Development and states as follows: "It is concluded that the methodology of add-on trials for this indication [bipolar disorder] requires further refinement and the inability to control potential confounding variables is a major limitation of this design. No further trials are planned with gabapentin in any psychiatric indications."

[4] *See* Frye et al., 2000; Pande et al., 2000a; Pande et al., 2000b; Obrocea et al., 2002

[5] Morello et al., 1999; Frye et al., 2000; Obrocea et al., 2002

[6] Graves, 1998

when the Food and Drug Administration (FDA) sent a letter to Parke-Davis warning them to stop promoting Neurontin for off-label uses.[7]

15. Indeed, off-label use of Neurontin continued until the Securities and Exchange Commission brought charges leading to an eventual guilty plea for illegal off-label promotion.[8] In May 2004, Warner-Lambert "agreed to plead guilty and pay more that $430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division's illegal and fraudulent promotion of unapproved uses" for Neurontin.[9] The Department of Justice release also noted "[p]otential problems that can arise from off-label use without the benefit of FDA oversight include the occurrence of unforeseen adverse effects because the drug was not studied in the type of patient it is being used for off-label and the appropriate dosage and course of treatment have not be established."[10] Despite this, off-label use of gabapentin continues to represent the majority of its use.[11]

[7] See V054645
[8] Department of Justice statement; May 13, 2004. Warner Lambert pled guilty to violations of the United States Code, Sections 331(a), 331(d), 333(a), 352(f)(l), and 355(a).
[9] See www.usdoj.gov/opa/pr/2004/May04_civ_322.htm
[10] See www.usdoj.gov/opa/pr/2004/May04_civ_322.htm.
[11] *See* Hamer et al., 2002; J Schmit, USA Today, August 16, 2004; Chen et al., 2005

III. SAFETY AND REGULATORY OVERVIEW

16. The Federal Food, Drug, and Cosmetic Act requires that pharmaceutical manufacturers comply with specific regulatory requirements when developing and marketing products (Federal Food, Drug and Cosmetic Act, Ch. V, 21 U.S.C. §§351-360bbb-3 (2005)). The Code of Federal Regulations (CFR) is a compilation of the regulations published in the Federal Register by the executive departments and agencies of the Federal Government. The CFR is divided into 50 titles that represent broad areas subject to Federal regulation; FDA regulations are published under Title 21. To assist pharmaceutical manufacturers in complying with these procedures and regulations, the FDA has issued a large number of general and specific Guidances. FDA Guidance documents represent the Agency's current thinking on a particular subject, and describe the minimum requirements for the registration and marketing of new drug products in the United States (MAPP 4000.2).

17. Before a new drug product can be marketed in the United States, a pharmaceutical manufacturer must independently conduct a wide variety of preclinical (21 C.F.R. §§ 314.50(d)(2)) and clinical (21 C.F.R. § 314.50(d)(3)(5)) studies to support the pre-marketing new drug application[12]. These include studies designed to assess the clinical safety and efficacy of the drug in the patient populations for whom the drug will be prescribed. Sponsors often additionally examine specific patient populations to determine if the proposed drug may have selective safety concerns in these patients (21 C.F.R. §§ 314.50(d)(5)(v).

18. The FDA does not and cannot independently guarantee the safety of any pharmaceutical product. Rather, a primary mission of the FDA is to promote the public health by promptly and efficiently reviewing clinical research and taking appropriate and timely action on the marketing of regulated products.

19. In order to assess pre-marketing risk, the FDA relies upon the manufacturer of a new drug product to conduct the appropriate preclinical studies and clinical trials. The manufacturer controls all of the critical elements relating to these trials, supplies the funding for the clinical trials, and provides the medications that are used. The drug manufacturer also selects and monitors the clinical investigators who conduct the trials. All clinical trial data are submitted directly to the manufacturer. In a similar manner, the required preclinical trials are also conducted and controlled by the manufacturer. When completed, the preclinical and clinical trial data are compiled and reported to the FDA by the manufacturer. The FDA relies on the manufacturer to present a scientifically fair and balanced view of the drug sought to be approved, in much the same way that the IRS relies on taxpayers to present an honest and open report of their income to the government (21 C.F.R. § 314.50(e); 21 C.F.R. § 201.57). This labeling is developed based on the information provided by the sponsor and should be designed to convey all necessary prescribing and safety-related information. It is not uncommon for professional labeling to also include safety-related information for products with similar chemical compositions.[13]

20. It must be stressed that the FDA does not maintain its own preclinical and clinical testing laboratories, and does not conduct government-sponsored studies to independently evaluate the drug products or verify preclinical or clinical data. Rather, the Food, Drug, and Cosmetic Act gives FDA the responsibility to review clinical and preclinical research. Thus, the FDA relies upon the sponsors to conduct the proper preclinical and clinical studies and to report

[12] 21 CFR§ 314.50
[13] 21 CFR§ 201.57

the results accurately and completely. If the reports submitted by the sponsors were incomplete or inaccurate, the validity of an FDA approval, predicated upon such reported data, would be jeopardized.

21. An FDA approval also does not guarantee that a drug product will be safe for all time and for all purposes. A number of drugs have been approved by the FDA and then later withdrawn from the market because of emergent adverse medical events.[14] Both the FDA and the pharmaceutical industry therefore have very important responsibilities for monitoring adverse events after a new drug product has been launched.

22. To assist the FDA with post-marketing risk assessment, pharmaceutical manufacturers are required to establish a system for pharmacovigilance activities. Manufacturers must collect, collate and evaluate information about suspected adverse reactions, both here in the United States and worldwide (21 C.F.R. § 314.80). Section 314.80(c) indicates that pharmaceutical manufacturers "develop written procedures" for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.[15]

23. All relevant information, including reports and analyses of updated safety-related information, must be shared with the FDA. These safety data are derived from a variety of sources including the manufacturer's internal studies and reports, spontaneous domestic and international adverse event reports, ongoing U.S. and foreign trials, the clinical and preclinical literature and other available databases. When a possible safety signal is identified, it is suggested that manufacturers track and report safety-related information for similar products.[16]

24. Surveillance is critically important for the development of a safety database for the drug product.[17] Experience has taught that pre-marketing clinical trial data provide only initial and preliminary safety information for a new drug product. Frequently, critical safety concerns are not observed until after an approved product has been commercially launched. There are several reasons for the delayed appearance of adverse medical events. One reason is that a relatively small number of patients (usually only up to a few thousand) are actually exposed to a new drug before it is approved. As such, only the most frequently occurring adverse events will be observed. Following approval, a much larger population uses the drug and the less frequent adverse events will then be evidenced.

25. A second reason contributing to the delayed appearance of certain adverse medical events relates to the patients chosen for clinical trials. In general, with the exception of the disorder for which the drug is being studied, relatively healthy patients are enrolled in investigational drug trials. Moreover, most clinical trials will discontinue a patient if the precursor signals to an adverse experience are suspected. However, once a drug product is approved, it will be given to patients with additional illnesses and to patients receiving multiple other drug

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[14] *See* Clarke et al., 2006.

[15] *See* deposition of Manfred Hauben (Medical Dir. Risk Management at Pfizer), July 13, 2007 at pp 444-445: "Q. So, does the company, Pfizer, have developed a written procedure for the receipt of post-marketing adverse drug experiences? . . . . A. Yes. . . . Q. Does the FDA tell you how you have to receive them? . . . . Does the FDA dictate to you how you're supposed to receive the reports? A. Well, the reports, we don't have control over the reports being sent to us, so the receipt process is not in our control. What's in our control is what happens after receipt. Q. And in a nutshell, whatever the standard operating procedures that Pfizer has regarding the receipt or evaluation and reporting, would you agree that those standard operating procedures were promulgated by Pfizer, meaning Pfizer wrote them, not someone else? A. Yes."

[16] Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

[17] Strom, B. 2000, Pharmacoepidemiology: 3rd Edition; *See* p. 231.

products. Not surprisingly, these additional circumstances will often lead to the appearance of new adverse events, increases in the frequency of previously observed events and the emergence of new drug interactions.

26. A third reason for the delayed appearance of post-marketing adverse events is the time required for certain events to emerge. Many drug related events, including certain cancers or other delayed responses, may not be seen until several years of exposure to the offending agent has occurred.

27. Because the post marketing surveillance system provides safety data concerning real patients in a real world setting, it is a vital and integral component of the FDA's efforts to ensure the continued safety of marketed drug products. It is for this reason that the FDA relies on safety surveillance to track adverse drug experiences from the launch of a new drug product and throughout its entire marketing lifespan. Unfortunately, the extent of under-reporting of adverse events results in the surveillance system capturing only a fraction (approximately 1-10%) of the actual numbers of adverse events. It is therefore imperative that manufacturers closely monitor all available data, conscientiously review published literature, conduct necessary follow-up studies and fully explore all potential adverse events.

28. FDA has also noted that because of the unknown extent of under-reporting, comparison of baseline adverse event data between the drug-exposed population and a demographically-similar untreated population (i.e., those not using the drug) is not necessarily valid and does not eliminate the requirement for labeling additions relating to newly observed adverse events.[18]

29. Several factors contribute to the low percentage of significant adverse medical events actually reported to the FDA and to other authorities. A major factor is that many health care providers do not associate a patient's complaints or symptoms with a drug-related adverse event. Often times the new event is simply considered a component of the patient's medical condition or an unrelated concomitant illness. This is particularly likely to occur if representatives of the drug manufacturer fail to share all available label information with prescribers or make untrue or scientifically unbalanced presentations to prescribers. It is therefore critically important that drug manufacturers fully alert prescribers to potential adverse events and safety concerns with their products in all promotional materials. After all, physicians and other prescribers rely on drug company representatives to provide them with drug-related information.

30. Another factor contributing to the low reporting rate of adverse events is that many health care providers are simply unaware of the various programs developed to receive this information. Pharmaceutical organizations should assist FDA with their ongoing efforts to promote this important exchange of information. Finally, the great majority of adverse event reports are sent to and reviewed by the manufacturer of the drug product, who is then required to submit data relevant to these reports to the FDA. If a manufacturer inaccurately, incompletely, or inarticulately submits adverse event reports and subsequent analyses, the FDA may not fully appreciate an emerging or changing safety profile associated with a drug product.

31. A safety signal, as defined by FDA, "*refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use.*"[19] FDA's post-marketing surveillance requirement is in place to detect new safety signals associated

[18] *See* FDA Alert for Healthcare Professionals, Isotretinoin November, 2005.
[19] *See* Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

with the use of a drug product which may not have been detected in the pre-marketing clinical trials. The system also detects increases in the frequency or severity of previously identified events. If there is an *association* between the event and the drug product, additional or intensified labeling warnings relating to the newly identified event can be enacted. Once a signal is detected, the specific adverse events should be fully and quickly evaluated to determine if a new patient safety risk has been identified. The sponsor is then required to review this information to determine if additional scientific studies and regulatory actions are needed to address safety concerns. If the manufacturer and/or the FDA consider the new signal sufficiently serious, the drug product may be restricted to certain patients or even temporarily or permanently withdrawn from the U.S. marketplace.[20]

32. Importantly, the responsibility of the detection of "signals" in post marketing surveillance is that of the manufacturer. Although FDA may also receive reports of Adverse Drug Events (ADEs), the FDA does not have the resources to properly evaluate and act upon reports concerning thousands of marketed products. The first line of defense falls to the manufacturer of the product, and if the manufacturer fails in its duty, serious injury or death may occur. There is no magic number for the number of events needed to precipitate immediate action by the NDA holder. It does not have to include an explosion of events. There are examples of labeling changes and Dear Health Care Professional letters issued based upon a manufacturer's receipt of only two or three events.[21]

33. The obligation to report all safety related information includes serious ADEs occurring outside the country (21 C.F.R. § 314.80(b)). Manufacturers also have an obligation to report any intentional labeling changes to the FDA. The reporting of worldwide events is critically important because most safety issues are not dependent on nation or regional parameters. Foreign regulatory authorities must also be informed if FDA effects labeling changes or if new adverse event information has been identified in the United States.

34. Pharmaceutical manufacturers should continually amend their package inserts, professional labeling and promotional materials in response to new safety information (21 C.F.R § 314.70). Such safety information includes new ADEs or changes in the severity or frequency of previously identified events. These data may be derived from post-marketing reports, reports from clinical trials, ongoing studies or the clinical literature. Product information and labeling must be immediately modified and disseminated when serious clinical events are reported. All efforts must then be taken to ensure that the necessary information is expeditiously conveyed to health care professionals and consumers.

35. Prior to 2008, the FDA did not have the authority, mission or resources to require identification, evaluation and correction of all safety-related issues involving marketed drug products. In fact, prominent drug safety issues involving recently withdrawn products have called into question the capability and credibility of FDA's drug safety program, and have caused the Agency to seek a significant increase in budgeted resources for the Office of Drug Safety.[22] Both Congress and the Executive Office corrected this limitation with their recent renewal of the Prescription Drug User Fee Act (PDUFA) in September 2007. Prior to this, FDA did not have the authority to mandate post-approval safety studies or require changes to product labeling. However, beginning in 2008 FDA will have the legal authority to mandate and effect safety-related requirements.

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[20] *See* Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.
[21] *See* Dear Doctor Letter December 23, 1996, Somerset Pharmaceuticals, Eldepryl Capsules.
[22] Frantz, 2005

IV. NEURONTIN® (GABAPENTIN) SAFETY AND REGULATORY HISTORY

36. Neurontin (Gabapentin) was approved in the United States in December 1993 as an adjunctive therapy for the treatment of partial seizures in adults (NDA 20-235). Clinical studies of Neurontin administered either as add-on therapy or monotherapy for the management of epilepsy have been conducted in the US and internationally since 1984. Approval for the same use in pediatric epilepsy patients was granted in October 2000. Pfizer Defendants attempted to gain a monotherapy indication for Neurontin® but this submission was deemed not approvable by the FDA due to insufficient demonstration of efficacy. In May 2001, an attempt to gain Neurontin approval for use in generalized neuropathic pain conditions was also denied by FDA due to insufficient data.[23] Subsequent to this, Pfizer Defendants secured approval for the restricted indication of neuropathic pain associated with post herpetic neuralgia only (May 24, 2002). In the U.S., Pfizer currently markets Neurontin tablets (NDA #20-882), capsules (NDA #20-235) and oral solution (NDA #21-216) for the two approved indications.

37. The regulatory history of Neurontin was examined, including available safety data and corresponding "safety signals" with particular attention to psychobiologic adverse events, and the Pfizer Defendants' actions (or inaction) in responding to such "safety signals". This information was reviewed by particular time-periods: pre-approval, 1994-1996, 1996-2002, and 2002 – present. These time-periods reflect important factual circumstances in the development and marketing of Neurontin that afforded the Pfizer Defendants the opportunity to take appropriate action and properly inform the FDA or prescribers of the association of psychobiologic adverse events, particularly suicidal behavior, with Neurontin use.

38. As more fully set forth in this report, the pre-approval stage of Neurontin revealed "safety signals" from Pfizer Defendants' pre-clinical and clinical trials including an *association* – by Pfizer Defendants' own admission --- of psychobiologic adverse events, including depression and suicidal behavior adverse events. During this stage, Pfizer Defendants' own Integrated Summary of Safety (ISS) for Neurontin demonstrated adverse events of clinically important depression that, as per FDA notice to Pfizer Defendants, limited the widespread usefulness of Neurontin outside of its very narrow approved indication for epilepsy; FDA was concerned that depression could become worse and result in suicidal behavior. A positive dechallenge/rechallenge reaction of depression was also observed in Pfizer Defendants' clinical trials and was deemed probably related to Neurontin by Pfizer Defendants' qualified investigators.

39. Similarly, the time period of 1994-September 1996 represented an important phase in the development and marketing of Neurontin. In particular, this period reflected Neurontin's initial use by the public. The time period also encompasses the Pfizer Defendants' illegal off-label promotion activities for which Pfizer Defendants would later plead guilty to various violations of federal law. Gabapentin was being used increasingly for indications for which it was not approved, including for a number of mood disorders. These patient populations are obviously considered more at risk for suicide-related events. During this time period, and as more fully set forth below, adverse events reported in various publications and data sources continued to reflect that gabapentin was associated with psychobiological events, where there were observed positive dechallenge events, as well as events occurring in healthy

[23] IND28454_MISC_005_0026-30

volunteers where there was a relationship between the events and increased exposures to gabapentin. Withdrawals from certain Pfizer Defendants' studies also reflected that approximately twice as many gabapentin patients (compared to placebo patients) withdrew as a result of clinically-related psychobiologic events. Moreover, Pfizer Defendants --- apparently cognizant of a safety signal of psychobiologic events --- commissioned only a perfunctory review of psychosis and behavioral disturbances in or about 1995. Finally, despite knowledge of Neurontin's increasing off-label use in populations with underlying depressive conditions, Pfizer Defendants failed to appropriately address or pursue language in the product labeling regarding Neurontin's mechanism of action to adequately inform healthcare professionals as to Neurontin's capacity to reduce the release of monoamine neurotransmitters in the brain (*e.g.*, serotonin, norepinephrine), an action that is implicated in the pathophysiology of clinical depression.

40. The time period October 1996 – May 2002 represents another stage in the development and marketing of Neurontin in which critical safety signals continued to escalate. Defendants also gained approval for the post herpetic neuralgia indication during this timeframe. However, the Pfizer Defendants failed to appropriately address or pursue updated language in the product labeling regarding Neurontin's mechanism of action to reduce the release of monoamine neurotransmitters in the brain (*e.g.*, serotonin, norepinephrine). These actions may contribute to psychobiologic adverse events, including suicidal behavior.

41. June 2002 through present day reflects, not only the continuing safety signals mentioned above, but also Pfizer Defendants' labeling change regarding suicide and suicide attempt and FDA's pending inquiry to Pfizer Defendants about Neurontin's capacity to contribute to suicidal behavior.

42. Pfizer Defendants failed to take appropriate action to recognize and respond to safety signals demonstrating an association between Neurontin use and psychobiologic adverse events, including depression and suicidal behavior. A more careful examination of these signals should have been undertaken and subsequently, changes to the product labeling should have been affected to reflect the rate and severity of these events. Moreover, Pfizer Defendants should have undertaken an educational campaign targeted to healthcare professionals and patients using neurontin, with particular attention to discouraging off label use.

43. As more fully set forth in this report, throughout the life of Neurontin's development and marketing, Pfizer Defendants possessed specific information indicating a lack of efficacy, particularly with certain off-label indications (*e.g.*, psychiatric/bipolar disorder). Pfizer Defendants failed to reasonably warn healthcare professionals of this lack of efficacy notwithstanding Pfizer Defendants' knowledge of Neurontin's widescale use for such indications.[24]

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[24] *See* Bernstein, *Enhancing Drug Effectiveness and Efficacy through Personal Injury Litigation*, Journal of Law and Policy (2007) at p.133: "Since safety is a context-driven condition, bound up with effectiveness --- even a small risk is too much when the drug is absolutely ineffective --- and because no prescription drug is perfectly safe, this black-letter necessarily takes effectiveness into account. And whenever consumers have more than one treatment to choose from, effectiveness cannot be divorced from comparisons with the drug's alternatives. To put the point within traditional warning doctrine, a crucial element of an adequate warning is communication about the consequences of not heeding it. Warnings are messages about choice. The risk reduction category of warning says, 'When you use our product, consider the following concurrent precaution, for the following reason.'"

IV(a) Psychobiological Adverse Events in Pre-Approval Stage

44. Neurontin's capacity to contribute to mood and behavioral disturbances, particularly depression and suicide-related behavior, was known to Pfizer Defendants prior to the product's approval by the FDA. Before Neurontin was approved by FDA in 1993, on December 14th and 15th, 1992**,** a meeting was held between Parke-Davis and the Peripheral and Central Nervous System Drugs Advisory Committee.[25] At that time, a total of 5 reports of overdose involving gabapentin were noted. Four cases involved patients in Neurontin clinical trials, who also ingested additional drugs. The other case involved the child of a study subject who ingested gabapentin only. None of these patients died.

45. In the total exposed population of the NDA there were 78 reports of depression (or 5.3% of the patients).[26] There were 7 reports of depression as a serious adverse event and 9 patients withdrew from studies because of depression, some of which had suicidal ideation (no number was provided for this). It was determined that of the 78 patients reporting depression, 19 had no prior history and 22 patients required treatment for their symptoms. In the transcript to the Advisory Committee Meeting it is indicated that "*gabapentin has a safety profile that is generally good, but … there remain some concerns*."[27] FDA approval for gabapentin was received on December 30, 1993.

46. Regulatory documents from the FDA reflect Pfizer Defendants' knowledge about Neurontin's capacity to contribute to mood and behavioral disturbances, including depression and suicidal behavior. Prior to approval for use as adjunctive medication in refractory partial epilepsy, the FDA via the Division of Neuropharmacological Drug Products prepared a combined medical-statistical review.[28] As part of this clinical safety review, FDA reviewed portions of Pfizer Defendants' New Drug Application (NDA). The FDA concluded that "**[l]ess common but more serious events may limit the drug's widespread usefulness…. [D]epression, while it may [not be] an infrequent occurrence in the epileptic population, may become worse and require intervention or lead to suicide, as it has resulted in some suicide attempts.**"[29] FDA further stated the following:

> In its clinical database of 2048 patients, gabapentin has a risk profile that is uncertain, with five groups of important adverse events that have not yet been fully characterized, specifically, seizure exacerbation, carcinogenicity, **clinically important depression**, renal failure and teratogenicity. Accumulated long range safety data are limited by the excessive attrition due to apparent lack of sustained efficacy. . . . In conclusion NDA 20-235 is approvable with appropriate and prominent labeling for use in a specific population.[30]

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[25] Dept. of Health and Human Services, Public Health Services, FDA, Peripheral and Central Nervous System Drugs Advisory Committee Transcript (Vol. II, Dec. 15, 1992); *see also* Deposition of Lloyd Knapp, at Ex. 7 (July 18, 2006).

[26] Dept. of Health and Human Services, Public Health Services, FDA, Peripheral and Central Nervous System Drugs Advisory Committee Transcript (Vol. II, Dec. 15, 1992 at p.58); *see* NDA #20-235 Medical-Statistical Review, at 114.

[27] Dept. of Health and Human Services, Public Health Services, FDA, Peripheral and Central Nervous System Drugs Advisory Committee Transcript (Vol. II, Dec. 15, 1992 at p.59).

[28] NDA #20-235 Medical Statistical Review.

[29] NDA #20-235 Medical Statistical Review, at p.117.

[30] NDA #20-235 Medical Statistical Review, at pp. 117, 119.

47. The FDA medical-statistical review encompassed the Pfizer Defendants' NDA and included Pfizer Defendants' First and Second Safety Updates that were submitted on May 29, 1992 and November 2, 1992, respectively. After submission of the Third Safety Update, FDA clinical reviewer Cynthia McCormick, MD, stated on September 27, 1993, that "There are no new data in Safety Update #3 which alter the safety profile of this drug as presented in the initial NDA and Safety Update #1 and 2."[31] Thereafter, subsequent to the submission by Pfizer Defendants of the Fourth Safety Update, FDA clinical review Cynthia McCormick, MD, similarly stated, "There are no new data in the Safety Update #4 which alter the safety profile of this drug as presented in the initial NDA and Safety Update #1, 2, and 3."[32] Despite FDA observations relating to depression and other psychobiological events, Pfizer Defendants failed to take appropriate actions to warn or further evaluate Neurontin-precipitated mood and behavioral disturbances, including depression and suicidal behavior.[33]

48. Among the documents and data reviewed also include Pfizer Defendants' Integrated Summary of Safety (ISS) and relevant appendices submitted by Pfizer Defendants in their original New Drug Application (NDA) for Neurontin. The ISS reflects the Pfizer Defendants' comprehensive summary of 35 clinical pharmacology and 35 clinical studies involving 1797 participants, 1748 of whom received Neurontin.[34] Unfortunately, the accumulation of suicide-related events experiences in the premarketing period are not fully described and summarized in the Defendants submissions.

49. The ISS documents diluted the significance of self-injurious psychobiological adverse events observed in the clinical trials. For example, the Pfizer Defendants employed coding conventions which convey underestimations of the seriousness of the observed self-injurious events. These include reports described from trials 877-210P and 945-013.

50. Additionally, suicide-related events were not adequately described in the ISS and some events were not corrected until provided to FDA when specifically requested to do so in 2004. These include patients from trials 945-013 and 945-015.

51. Finally, a scientifically concise summary of these suicide-related events was not provided by the Pfizer Defendants. While they did state in Safety Update #4, that "…the cumulative total of patients who experienced depression with suicide ideation or suicide attempt [is] ten.", a more detailed discussion of suicide-related events and the inclusion of an appropriate language in the Neurontin product labeling would have been more instructive.

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[31] Pfizer_Lalphs_0084480 at 0084498.

[32] Pfizer_Lalphs_ 0084680 at 0084687.

[33] Noteworthy, subsequent to Dr. Cynthia McCormick's combined medical-statistical review mentioned above, Dr. Russell Katz (FDA Division of Neuropharmacological Drug Products) on October 11, 1993 provided a memorandum in which he summarized the more common adverse reactions during clinical trials that resulted in the dropout from clinical trials: Depression and Suicidal Ideation ranked 9th (10/2048) among such adverse reactions. *See* Pfizer_LLamoreaux_0031285 at 0031300. A review of Pfizer Defendants' proposed responses to inquiries regarding Neurontin does not reflect that Pfizer Defendants responded to an inquiry about depression or suicidal behavior with any reference to the combined medical-statistical review or Dr. Katz's memorandum. Apparently, these documents are available only based upon Freedom of Information (FOI) Requests to the government; there is no indication that Pfizer Defendants would (or have) made this documents available as part of Standard Response Documents (e.g., Medical Information Department responses to inquiries) or as par of Dear Healthcare Professional letters. *See* Pfizer_LLamoreaux_0031285 (Memo from Parke-Davis employee Janith Turner, dated July 28, 1994, entitled FDA FOI Documents for Neurontin NDA Approval).

[34] RR-REG 720-02957

Dechallenge and Rechallenge Events

52. Psychobiological events involving dechallenge and rechallenge data associated with Neurontin use were not fully described in the ISS documents or disclosed in the Neurontin launch label.

53. If an adverse event that develops following the initiation of drug therapy subsequently resolves following the discontinuation of the drug, this is referred to as a positive dechallenge. A positive rechallenge refers to the re-occurrence of the adverse event (following a positive dechallenge) subsequent to re-initiation of the drug.

54. The FDA places great significance on dechallenge/rechallenge observations and these events are often included in product labeling to assist prescribers and patients with benefit/risk assessments. As such, the dechallenge/rechallenge psychobiological events described in conjunction with Neurontin use should have been incorporated into the labeling.[35] Such incorporation into the labeling would have been consistent with FDA guidelines. The following description of serious adverse events can be found in the *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (*July 1988*), a document prepared by the Center for Drug Evaluation and Research (FDA) and intended to be used as a guide for the formatting of a New Drug Application (NDA): "***It may not, indeed often will not, be possible to decide whether a particular serious event is drug-induced, but such events should be noted for future review and consideration in the post-marketing period and perhaps identified in labeling as a possible adverse effect of uncertain relationship to the drug. Steps planned to evaluate adverse events further should be noted."***

55. It is not necessary to have significant numbers of dechallenge/rechallenge events to appreciate drug toxicities. For example, in the March 2005 Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA notes the following: "*It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug*".

56. Publications contributed by FDA authors also note that dechallenge/rechallenge data are useful for causation considerations.[36]

[35] Temple et al., 1979; Strom 2000 Pharmacoepidemiology, 3rd Edition

[36] See Temple *et al.*, 1979; See also Strom, BL, 2000 Pharmacoepidemiology, Chapter 10 (Kennedy, DL, Goldman, SA & Lillie RB, *Spontaneous Reporting in the United States*)

57. Incidences of positive dechallenge/rechallenge events have been documented in clinical trials involving gabapentin. Dechallenge events include suicidal ideation, depression and hostility. In addition, a positive rechallenge event was documented in one patient (depression).

58. Original patient narratives relating to dechallenge events are outlined below. **In one particular instance there was a well-documented case of dechallenge/rechallenge.** A patient (Patient 1-1 from Study 945-015, RR #720-02837) receiving gabapentin became severely depressed and had suicidal ideations while on the drug. **When gabapentin was tapered and subsequently discontinued, the patient recovered from both the depressive and suicidal events. Upon readministration of gabapentin (rechallenge) the patient again became depressed.** "**The investigator considered the event probably related to gabapentin therapy, and the patient was withdrawn from the study."**[37] This event should have been highlighted in a separate section of the Pfizer Defendants' ISS and discussed in detail with the additional patients who expressed suicidal ideations or attempted to take their own life. Examples of positive dechallenge/rechallenge events related to psychobiologic function and associated with Neurontin are provided below (a-g). All of these events occurred prior to the December 1993 approval of Neurontin.

a. Research Report #RR-X-4300-00003 June 9, 1986
Positive dechallenge: **reactive depression (1)**

> Psychological symptoms of "depression/depressed feeling" were reported in 3/57 patients of unknown origin: 2 under baseline SAEDs and 1 patient under 600 mg gabapentin (possibly reactive depression) lasting 1.5 months during the dosage reduction period (following completion of the treatment phase up to 1200 mg) which completely disappeared in the one month follow-up phase after washout of gabapentin.

[37] RR 720-02837 (emphasis added) at p. 94-95. Pfizer Defendants' causal association assessment ranged from Definite, Probable, Possible, or of Unknown Relationship. *See* RR 720-02837 at p.67. Additionally, Pfizer Defendants also appear to have utilized Causality Assessments based on Karch, F.E. and Lasagna, L., JAMA 234, 1236-1241 (1975) as it pertained to such open-label studies of the safety and efficacy of gabapentin (Protocol 945-15). *See* Pfizer_LLaMoreaux_0018652 at 0018671. The criteria for assessment of causality (using Karch and Lasagna's approach) included Definite, Probable, Possible, Remote, and Unclear. Under these circumstances, the adverse event of depression regarding Patient 1 should have been coded more conservatively as Definitely Related. Definite is defined as "[a] reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues. Improvement or disappearance on stopping or reducing the dosage (dechallenge), [and] Reappearance of the reaction on repeated exposure (rechallenge)." Pfizer_LLaMoreaux_0018652 at 0018671.

b. Research Report # 4301-00124 September 12, 1991
Positive dechallenge: **hostility (1)**

> Patient 10 (Center 37), a 17-year-old man, had hyperkinesia (hyperactivity) and hostility (aggressive behavior) from Day 31 of gabapentin administration. The investigator considered these events moderate in intensity and probably related to gabapentin treatment (1200 mg/day), and the patient was withdrawn on Day 70. Mild hyperkinesia (900 mg/day) had previously occurred from Day 19 through Day 31, at which time intensity increased. Other adverse events were not reported. The hyperkinesia and hostility resolved on Day 76. Concurrent medications included valproate and phenytoin.

c. Research Report # RR 720-02816 September 10, 1991
Positive dechallenge: **depression (1)**

> Patient 205 (Center 10), a 30-year-old white woman in the gabapentin/gabapentin group, became depressed on Study Day 2 while receiving 1200 mg/day of gabapentin. The investigator considered this event mild and of unknown relationship to gabapentin. The depression became moderate and possibly related to gabapentin on Study Day 57. No concurrent medications were given for the depression and the gabapentin dosage remained unchanged until Study Day 93, when the patient was withdrawn from the study. Taper was completed on Study Day 97, and the depression resolved on Study Day 105. Medical history included hysterectomy, headaches, and urinary bladder repair. Concurrent medications included hydrochlorothiazide, estrogen, prednisone,

d. Research Report # 720-02837 September 6, 1991
Positive dechallenge: **depression/suicidal ideation**

Positive rechallenge: **depression (1)

Patient 1 (Center 1), a 36-year-old white man, experienced depression of moderate intensity on Day 12 while receiving 1500 mg/day gabapentin. Other concurrent adverse events were headache of severe intensity and diplopia of moderate intensity. The investigator stated that the patient had been depressed for two years prior to the study, but that the condition had worsened when headaches became severe in intensity. The headaches were position dependent; they resolved when the patient was supine, but they were severe in intensity and incapacitating when the patient was sitting up. The patient also had dizziness and nystagmus beginning on Days 20 and 22, respectively. The patient was hospitalized due to severe headache on Day 22. A spinal tap, CT scan, MRI, and arteriogram performed during this hospital stay were negative. Elevated serum concentration of carbamazepine was noted, and dosage was reduced from 2800 to 2600 mg/day. Gabapentin dosage was not changed. The patient was discharged on Day 24 with resolution of dizziness and nystagmus; however, headache, diplopia, and depression were continuing. The patient was referred for neurosurgical consultation. Medical history included a draining temporal arachnoid cyst diagnosed at age 33 and placement of a cystoperitoneal shunt two years later. Headache, also beginning at age 33, was treated with aspirin, ibuprofen, acetaminophen/codeine, and indomethacin during the study. Hypertension was present at screening, and blood pressure remained at 160/100 before and during the study despite treatment with verapamil and lisinopril. Treatment with verapamil began on Day 18 and treatment with lisinopril began on Day 30. Hospitalization occurred for a second time on Days 61 to 62 when an angiogram was performed. On Day 71, ongoing depression changed from moderate to severe intensity, and the patient also experienced suicidal ideation of severe intensity. Both events were judged clinically important by the investigator and possibly related to gabapentin treatment. Gabapentin treatment was tapered beginning on Day 85 and temporarily stopped on Day 111. Depression and suicide ideation resolved by Day 111, although headache continued. During Days 226 to 231, while off gabapentin therapy, the patient was hospitalized for revision of a left cystoperitoneal shunt, and headache resolved. The patient was rechallenged with gabapentin on Day 267. Depression reoccurred on Day 271, and became severe on Day 295. The investigator considered the event probably related to gabapentin therapy, and the patient was withdrawn from the study. The last dose of gabapentin was given on Day 300. Depression, diplopia, and nystagmus were continuing at the last visit.

e. Research Report # 720-02883 August 16, 1991
Positive dechallenge: **depression**

Patient 213 (Center 1), a 46-year-old white female, became depressed on Day 294 while receiving 2400 mg/day of gabapentin. The investigator considered this event of moderate intensity and possibly related to study drug, but no changes in study medication were made at this time. On Day 433 the investigator felt that the depression had changed in intensity to severe and designated it as a clinically important adverse event. At this time, the patient was permanently discontinued from further gabapentin treatment. The taper was completed on Day 438. The patient's past medical history included a tubal ligation and a hysterectomy. Other adverse events during the study included insomnia, upper respiratory infection, and blurred vision. Concurrent medications included norephedrine, guaifenesin, and conjugated estrogens. Concurrent AEDs included carbamazepine (1200 mg/day) and clorazepate (15 mg/day). The patient's depression resolved on Day 447.

f. Research Report # 720-02883 August 16, 1991
Positive dechallenge: **depression**

Patient 107 (Center 4), a 29-year-old white male, entered the present study with amnesia, impotence, and depression that had begun in the preceding studies (945-5 and 945-5X) on Days 14, 68, and 147 of gabapentin therapy, respectively. The patient was receiving 1200-1800 mg/day of gabapentin at the time the events began. The investigator considered all three of these events mild and possibly related to the study medication. These problems continued in the extended open-label protocol as the gabapentin dose was increased to 2000 mg/day on Day 168 and to 2200 mg/day on Day 190. On Day 217 the patient was permanently discontinued from the study and the gabapentin taper was complete on Day 238. The memory problems and depression resolved on Day 239 but the resolution of the impotence was unknown. The patient's past medical history is listed in the appendix. Concurrent medications included ibuprofen, bismuth subsalicylate, acetaminophen, and cholestyramine. Concurrent AEDs included carbamazepine (1600 mg/day) and primidone (750 mg/day). Because this patient was withdrawn from the study as a result of adverse events that were not TESS, he is not included in the total number of patients withdrawing due to adverse events in Appendix B.53.

g. Research Report # RR 720-02993 September 13, 1991
Positive dechallenge: **hostility (1)**

> Patient 102 (Center 211), a 21-year-old man, completed the double-blind phase of the study in the placebo group and began gabapentin treatment as open-label therapy. From Day 20 of gabapentin administration (1200 mg/day), the patient experienced dizziness (drunk feeling) and hostility (aggressive behavior). The investigator considered these events mild in intensity and possibly associated with gabapentin treatment. Tapering for gabapentin discontinuation began on Day 30, and the last dose of gabapentin was taken on Day 37. The dizziness and hostility resolved on Day 34. This patient was also receiving carbamazepine and phenytoin.

CONCLUSIONS – NEURONTIN PREAPPROVAL STAGE

59. It is clear that self-injurious behaviors, including suicide-related events associated with Neurontin, were evidenced in the clinical trial data generated in support of the initial Neurontin approval. Available biochemical and pharmacology data supported the biological plausibility of these observations (*e.g.*, Research Reports #740-02959 and #740-03075). As such, the Pfizer Defendants were placed on notice of these events and should have carefully monitored postmarketing reports associated with Neurontin upon product launch, especially those reports related to psychobiologic function and suicide-related behavior.

IV(b) Psychobiological Adverse Events in Post-Marketing Stage: 1994-1996

60. In addition to reviewing the psychobiological adverse events that occurred during the pre-approval phase (*e.g.*, the period from initial clinical testing with gabapentin (mid 1980's) through the time of its approval for the adjunctive treatment of epilepsy (December 1993), the frequencies and severities of psychobiological adverse events in the initial years following market launch (January 1994 through September 1996) were also examined.

61. In examining the Pfizer Defendants' activities regarding Neurontin during the 1994-1996 timeframe, data, information and adverse event reports from multiple sources including internal Pfizer Defendant documents (Research Reports, Annual Reports, Periodic Safety Update Reports, internal adverse event database); adverse event databases (the United States FDA Spontaneous Reporting System; the World Health Organization, WHO); clinical and scientific literature and other sources were reviewed.

62. Clinical studies of gabapentin were conducted in the United States and internationally by the Defendants. The time period review from 1994-1996 encompasses the time immediately following the approval of gabapentin for adjunctive treatment of epilepsy through the completion of the large STEPS (Study of Titration to Effectiveness and Profile of Safety) trial (September 1996).

NEURONTIN CLINICAL PHARMACOLOGY STUDIES

63. Nine clinical pharmacology studies conducted/sponsored by Pfizer Defendants provide data for this section and a description of each study is provided. Eight of the nine studies were performed in adults, 7 of which were in healthy volunteers. Six of the nine studies examined single doses of gabapentin and in 2 of these studies psychobiologic adverse events were observed. Psychobiological adverse events were observed in two of the three multi-dose studies.

64. As noted in the following Tables, there were a variety of psychobiological adverse events, though there were no reports of depression, hostility, or suicidal behaviors. There were no deaths, withdrawals or serious adverse events with gabapentin treatment in any of these studies. Depersonalization was reported in three of the five studies reporting psychobiological adverse events.[38] Further, abnormal thinking and depersonalization were the two most frequently reported psychobiological events. These findings are particularly concerning in healthy volunteers receiving either one dose of gabapentin, or (at most) repeated doses for short periods of time.

65. A notable increase in the incidence of psychobiological events was observed in study 945-195, which used a high dose of gabapentin (2400 mg/day) for several weeks. This finding suggests that higher doses of gabapentin coupled with increased exposure may lead to increased incidences of psychobiologic adverse events.

[38] Depersonalization is an event often considered a preliminary event to suicidal behavior (Kelly and Knudson, 2000).

Overview of all Psychobiological Adverse Events

Studies[a]	***# Subjects/Patients***[b]	***Psychobiological AE's (# events)***	
CLINICAL PHARMACOLOGY STUDIES			
Total # of Studies (9)	240	Abnormal Thinking	16
		Depersonalization	11[c]
		Euphoria	6
		Confusion	5
		Nervousness	4
		Hyperkinesia	3
		Agitation	2
		Personality Disorder	2
		Abnormal Dreams	2
		Emotional Lability	1

[a] Studies completed or ongoing during the observed time period (January 1994 through September 1996) were included in the analysis

[b] number of subjects/patients receiving at least one dose of gabapentin

[c] Note the high number of depersonalization events in these studies. Depersonalization has been considered a precursor to suicidal thoughts (Kelly and Knudson, 2000). The fact that this event occurred in predominantly healthy subjects provides further evidence that caution is warranted in patient populations susceptible to this and other psychobiologic events

CLINICAL PHARMACOLOGY STUDIES

Single Dose Studies

Study #	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-188 (724-00222)	A study in healthy volunteers to determine the taste acceptability of 3 gabapentin (CI-945) liquid formulations (945-188-0)	1-5-94 to 11-11-94	None
945-189 (744-00249)	A single-dose bioequivalence study comparing 600-mg CI-945 tablets to 300-mg gabapentin Supro capsules (945-189-0)	4-17-95 to 4-28-95	Abnormal thinking {3}; Nervousness {2}; Euphoria {2}; Depersonalization {1}; Confusion {1}
945-196 (744-00309)	A single-dose study of Neurontin (gabapentin; CI-945), pharmacokinetics in healthy lactating women and evaluation of gabapentin concentrations in breast milk (945-196-0)	2-4-95 to 2-6-95	None
945-208 (744-00328)	A single-dose bioavailability study comparing 800-mg CI-945 tablets to 400-mg gabapentin supro capsules (945-208-0)	3-5-96 to 3-28-96	Emotional lability {2}; Thinking abnormal {3}; Personality disorder {1}; Abnormal dreams {***2, one unrelated***}; Depersonalization {1}
945-202-0 (744-00377)	A Single-Dose Study of Neurontin (Gabapentin; CI-945)Pharmacokinetics in Healthy Pediatric Subjects	12-9-95 to 12-10-95	None
945-072 (720-03359)	Open study for quantitative determination of gabapentin concentrations in pancreatic tissue and plasma following intravenous administration of gabapentin to patients undergoing pancreatic surgery (945-72)	7-20-92 to 8-19-93	None

*Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted

CLINICAL PHARMACOLOGY STUDIES *(continued)*

Multiple Dose Studies

Study #	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-190 (744-00238)	A multiple-dose, dose-proportionality study of Neurontin (gabapentin; CI-945) capsules in healthy volunteers (945-190-0)	1-23-95 to 2-27-95	Depersonalization {9}; Abnormal thinking {6}; Euphoria {4}; Hyperkinesia {3}; Agitation {2}; Nervousness {2}; Confusion {1}; Personality disorder {1}
945-430-005 (430-00110)	Comparison of gabapentin, carbamazepine, and placebo in a randomized, blinded 3-way crossover psychometric study in healthy volunteers (945-430-005, NE005)	10-21-94 to 8-15-95	None
945-195 (995-00072)	Double-Blind, Randomized, Two Period Crossover Comparison of the Cognitive and Behavioral Effects of Gabapentin and Carbamazepine in Healthy Adults	11-29-95 to 2-18-98	Thinking abnormal {4}; Confusion {3}

*Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted.

NEURONTIN MONOTHERAPY STUDIES

66. Seven (of 8 total) epilepsy monotherapy studies were completed during the period 1994-1996. A total of 989 patients received gabapentin in these completed trials. To date, Pfizer has not received FDA approval for the monotherapy indication in the U.S., and the enclosed studies do not provide data to support gabapentin's efficacy for this use.

67. An integrated across-study tabular summary of the psychobiological adverse events occurring in all completed epilepsy monotherapy trials is provided. The five most frequently-occurring psychobiological adverse events observed in all completed monotherapy trials were nervousness, thinking abnormal, confusion, emotional lability and depression. Depersonalization was reported in one patient from these trials. A total of 9 positive dechallenge reactions related to psychobiologic function were observed in 6 gabapentin patients participating in monotherapy studies. These events included reports of depression, hostility and hypomania.

Psychobiological Adverse Events in Monotherapy Trials

Studies[a]	***# Patients***[b]	***(# events)***
CLINICAL EPILEPSY STUDIES		
Monotherapy Studies (8)	1133*	Nervousness 58
*This includes both completed and ongoing studies		Thinking Abnormal 37
		Confusion 29
		Depression 27
		Emotional Lability 26
		Anxiety 24
		Agitation 8
		Hostility **7**
		Doped Feeling 6
		Euphoria 5
		Hallucinations 4
		Psychosis 4
		Suicide Attempt ***2***[c]
		Personality Disorder 2
		Apathy 1
		Depersonalization 1
		Overdose 1
		Abnormal Dreams 1
		Feeling High 1
		Feeling Abnormal 1
		Frustration 1
		Hypomania 1
		Paranoia 1
		Psychiatric Disorder 1
		Schizophrenic 1
		Suicidal **1**
		Withdrawal Syndrome 1

[a] Studies completed or ongoing during the observed time period (January 1994 through September 1996) were included in the analysis

[b] number of patients receiving at least one dose of gabapentin

[c] Events that ***should*** have been coded as suicide attempts

68. Although one patient receiving monotherapy was listed as being suicidal (945-083), 2 instances of suicide attempts were found in this trial (945-083). The patient listed (by Pfizer Defendants) as suicidal, actually attempted to kill himself (this should have been coded as a suicide attempt). The additional suicide attempt was coded (by Pfizer Defendants) as an overdose.

69. One monotherapy study was ongoing during the period under review. This study (945-092) was initiated in February 1995 and was completed in January 1998. Adverse events noted for this trial may thus have not occurred during the period January 1994 through September 1996. A total of 144 patients received gabapentin in this trial. Adverse psychobiologic events observed during this trial include reports of depression, thinking abnormal, anxiety, confusion, emotional lability and psychiatric disorder. It is important to note that gabapentin was less effective than the active comparator drug (carbamazepine).[39]

[39] *See* Study 945-092 (RR 720-04229), entitled "Gabapentin Monotherapy Trial: A 36-Week Double-Blind, Parallel-Group, Multicenter, Comparative Study of the Efficacy and Safety of Gabapentin Versus Carbamazepine in Patients with Partial Epilepsy (Protocol 945-092). The clinical trial dates encompassed February 2, 1995 through January 3, 1998, and adverse events associated with Neurontin included the following: Nervousness {***5***, ***three unrelated***}; Depression {***3***, ***one unrelated***}; Thinking Abnormal {***4***, ***one unrelated***}; Anxiety {***3***, ***two unrelated***}; Confusion {2}; Emotional Lability {1}; Psychiatric Disorder {***1***, ***unrelated***}. Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted.

CLINICAL STUDIES – EPILEPSY MONOTHERAPY (Completed Studies)

Study #	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-077 (720-03779)	A double-blind, dose-controlled, multicenter study comparing 3 doses of gabapentin (CI-945, Neurontin) administered as monotherapy and open-label carbamazepine in patients with newly diagnosed epilepsy: titration and evaluation phases (protocol 945-077 (international)	7-13-93 to 7-29-96	Confusion {1}; Nervousness {***9***, ***two unrelated***}; Depression {***4***, ***one unrelated***}; Anxiety {***2***, ***both unrelated***}; Thinking Abnormal {***2***, ***one unrelated***}; Euphoria {2}; Hostility {***2***, ***both unrelated***}; Emotional Lability {***2***, ***one unrelated***}; Withdrawal syndrome {***1***, ***unrelated***}; Abnormal dreams {***1***, ***unrelated***}
945-177 (720-03847)	Combined safety data from two double-blind, dose-controlled, multicenter study comparing 3 doses of gabapentin (CI-945, Neurontin) administered as monotherapy and open-label carbamazepine in patients with newly diagnosed epilepsy: titration and evaluation phases (945-077, 945-177)	7-13-93 to 7-29-96	Depression {1}; Anxiety {***2***, ***one unrelated***}
945-082 (720-03495)	A 26-week, double-blind, dose-controlled, multicenter study of conversion from marketed antiepileptic drug therapy to gabapentin (CI-945, Neurontin) monotherapy in patients in patients with complex partial or secondarily generalized seizures (protocol 945-082, US & Canada)	12-15-92 to 2-23-95	Nervousness {***18***, ***seven unrelated***}; Thinking Abnormal {***10***, ***three unrelated***}; Emotional Lability {***9***, ***one unrelated***}; Confusion {***8***, ***one unrelated***}; Depression {***8***, ***two unrelated***}; Anxiety {***6***, ***two unrelated***}; Agitation {1}; Apathy {1}; Depersonalization {***1***, ***unrelated***}; Frustration {1}; Paranoia {***1***, ***unrelated***}
945-088 (720-03675)	Gabapentin inpatient monotherapy trial: a double-blind, dose-controlled, multicenter study in patients with refractory partial epilepsy (945-88, US, Canada)	2-10-94 to 8-9-95	Psychosis {***2***, ***both unrelated***}; Anxiety {1}; Confusion {***1***, ***unrelated***}; Feeling High {1}; Hallucination {***1***, ***unrelated***}; Thinking Abnormal {1}

*Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted.

CLINICAL STUDIES – EPILEPSY MONOTHERAPY (Completed Studies - *continued*)

Study #	Title	Trial dates	Psychobiologic Adverse Events (Gabapentin)
945-083 (720-03497)	Interim report of an extended open-label, multicenter, safety and efficacy study of gabapentin (CI-945, Neurontin) monotherapy following a double-blind study (Protocol 945-082) in patients with complex partial or secondarily generalized seizures (Protocol 945-083)	5-22-93 to 8-31-95	Nervousness {***23***, ***seven unrelated***}; Thinking abnormal {***17***, ***four unrelated***}; Emotional Lability {***12***, ***nine unrelated***}; Depression {***11***, ***six unrelated***}; Confusion {***10***, ***five unrelated***}; Anxiety {***10***, ***six unrelated***}; Agitation {***5***, ***three unrelated***}; Hostility {***5***, ***two unrelated***}; Doped feeling {***5***, ***two unrelated***}; Psychosis {***1***, ***unrelated***}; Euphoria/high {3}; Apathy {1}; **Suicide Attempt {2}**[#]; Suicidal {***1***, ***unrelated***}; Depersonalization {1}; Hallucinations {***1***, ***unrelated***}; Schizophrenic {***1***, ***unrelated***}; Hypomania/overdose {1};
945-089 (720-03677)	Interim report of a 26-week, open-label, multicenter, safety and efficacy study of gabapentin (ci-945, Neurontin) monotherapy following a double-blind inpatient study (protocol 945-088) in patients with refractory partial epilepsy (protocol 945-089, US and Canada)	2-13-94 to 8-31-95	Confusion {3}; Nervousness {3}; Emotional Lability {2}; Thinking Abnormal {2}; Agitation {1}; Hallucination {1}; Psychosis {***1***, ***unrelated***}
945-36; 945-13-14 (720-03733)	A double-blind, single-center, 3-Way Crossover Study in patients with refractory partial seizures to determine the efficacy and safety of gabapentin monotherapy compared with carbamazepine monotherapy and gabapentin /carbamazepine combination therapy and follow-on open-label safety.	5-15-89 to 4-5-94	**Double-blind study:** Confusion {***2***, ***one unrelated***}; Emotional lability {5}; Thinking abnormal {3}; Nervousness {3}; Depression {***2***, ***one unrelated***}; Doped-up {1}; Psychosis {1} **Open-label study:** Confusion {***2***, ***one unrelated***}; Thinking Abnormal {***2***, ***one unrelated***}; Doped-Up {***1***, ***unrelated***}; Hallucinations {1}

2 suicide attempts should have been noted in this trial.

NEURONTIN ADJUNCTIVE (ADD-ON) THERAPY STUDIES

70. A total of 8 studies examining the efficacy of gabapentin as add-on therapy were either completed or ongoing during the period January 1994 through September 1996. Seven of these studies were completed prior to September 1996. Because the one ongoing study contained only 3 reports of psychobiologic adverse events (in 10 total patients receiving gabapentin) this review includes data from that study with the completed study data. Note also that one study, which failed to demonstrate efficacy (completed in 1991, initiated in June 1986) for which a Research Report was not published until 1994 (877-210G) is included. A total of 3235 patients received gabapentin in these studies. An integrated across-study tabular summary of the psychobiological adverse events occurring in all epilepsy add-on trials is provided below.

71. As noted, in the following Tables, the five most common psychobiological adverse events observed in all add-on therapy trials were nervousness, confusion, depression, thinking abnormal and emotional lability. Depersonalization was reported in one patient from these trials. A total of 6 positive dechallenge reactions related to psychobiologic function were observed in 6 gabapentin patients participating in these adjunctive therapy studies. These events included reports of confusion, nervousness and thinking abnormal.

Psychobiological Adverse Events in Add-on Therapy Trials

Studies[a]	***# Patients***[b]	***(# events)***	
Add-On Studies (8) *This includes both completed and ongoing studies	3235*	Confusion	57
		Nervousness	56
		Depression	38
		Thinking Abnormal	32
		Emotional Lability	20
		Anxiety	18
		Hostility	12
		Overdose	12
		Personality Disorder	12
		Agitation	10
		Euphoria	10
		Forgetfulness	8
		Depersonalization	7
		Hallucinations	5
		Giddiness	3
		Psychosis	3
		Suicide Attempt	***3***[c]
		Delirium	2
		Neurosis	2
		Paranoia	2
		Aggression	1
		Apathy	2
		Manic Reaction	1
		Mood Swings	1
		Suicidal	***1***[d]
		Suicide Attempt	**1**
		Suicide	**1**

[a] Studies completed or ongoing during the observed time period (January 1994 through September 1996) were included in the analysis

[b] number of patients receiving at least one dose of gabapentin

[c] Events that ***should*** have been coded as suicide attempts

[d] Event that ***should*** have been coded as suicidal

CLINICAL STUDIES – EPILEPSY ADD-ON THERAPY
(Completed and Ongoing Studies)

Study #	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-090 (995-00059)	A multicenter, randomized, double-blind, comparative study of gabapentin (CI-945) administered as an initial dosage of 900 mg/day versus a dosage titrated to 900 mg/day over three days (protocol 945-090)	6-6-94 to 6-8-95	Agitation {***3***, ***one unrelated***[#]}; Anxiety {***2***, ***one unrelated***}; Apathy {2}; Confusion {***13***, ***two unrelated***}; Depersonalization {4}; Depression {1}; Emotional lability {4}; Euphoria {7}; Nervousness {***18***, ***four unrelated***}; Neurosis {1}; Overdose {2}; Paranoia {1}; Thinking Abnormal {8}
945-423 (423-00110)	Open-label multicenter study to determine the percentage of patients with focal (partial onset) seizures, who are insufficiently controlled by antiepileptic monotherapy, becoming seizure free in at least one focal seizure type under add-on therapy with gabapentin	6-29-94 to 8-16-96	Depression {1}; Anxiety Attack {***1***, ***unrelated***}; Overdose {1}
945-430-004 (430-00112)	Double blind placebo controlled crossover study of the effects of three doses of Neurontin as add-on therapy in cognitive function of patients with epilepsy (protocol 945-430-004, NE004)	1-27-94 to 10-12-95	Aggression {1}; Mood Swings {1}; Anxiety {***1***, ***unrelated***}; Depression {***1***, ***unrelated***}
945-436-002 (436-000-072)	A multicenter, double-blind study comparing the safety and efficacy of gabapentin versus extended-release valproate sodium (depakine chrono) in 96 patients with partial seizures not controlled with carbamazepine	1-94 to 12-95	Depressive Syndrome {1}
945-462 (462-00008)	Open label multicenter uncontrolled 12 week study of efficacy and safety of gabapentin as add-on therapy in refractory partial epilepsy with or without secondary generalization	11-94 to 7-95	Forgetfulness {8}; Giddiness {3} (*Relationship of adverse events to gabapentin not provided in the Research Report*)

877-210G (720-03366)	A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of the Safety and Efficacy of Gabapentin (CI-945) as Add-On Therapy in Patients with Medically Uncontrolled Generalized Epilepsy	6-19-86 to 4-16-91	Agitation {2}; Anxiety {1}; Confusion {***2***, ***one unrelated***}; Depression {***2***, ***both unrelated***}; Emotional Lability {***4***, ***one unrelated***}; Hostility {1}; Nervousness {***2***, ***one unrelated***}
945-193; 945-200 (995-00057)	Neurontin STEPS (Study of Titration to Effectiveness and Profile of Safety) Plus Serum Gabapentin Levels	3-95 to 9-96	Overdose {***9***, ***six unrelated***}; Suicide Attempt {***1***, ***unrelated***; **should have been 2[#]**}; **Suicidal {1}**; Agitation {***5***, ***three unrelated***}; Anxiety {***14, four unrelated***}; Confusion {***41***, ***seven unrelated***}; Delirium {***2***, ***both unrelated***}; Depersonalization {3}; Depression {***33***, ***twenty-one unrelated***}; Emotional Lability {***12, three unrelated***}; Euphoria {***3***, ***one unrelated***}; Hallucinations {***5***, ***four unrelated***}; Hostility {***11, one unrelated***}; Manic Reaction {1}; Nervousness {***34***, ***seven unrelated***}; Neurosis {***1, unrelated***}; Paranoid Reaction {***1***, ***unrelated***}; Personality Disorder {***12***, ***two unrelated***}; Psychosis {***3***, ***all unrelated***}; Thinking Abnormal {***24***, ***two unrelated***}; Suicide {***1, unrelated***}
945-430003 (430-00120)	A Blinded Parallel Group Comparison of Neurontin (Gabapentin) and Sodium Valproate as Add-On Therapy in the Treatment of Partial Seizures	12-6-94 to 1-20-97	Nervousness {2}; Confusion {1}

*Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted

2 suicide attempts should have been noted in this trial.

STEPS Trial
(Study of Titration to Effectiveness and Profile of Safety)

72. The large, multicenter STEPS trial (Study of Titration to Effectiveness and Profile of Safety) was a Phase IV Postmarketing trial, performed (March 1995 through September 1996) to evaluate the safety and tolerability of gabapentin, the effect of gabapentin on the patient's quality of life and the relationship between gabapentin dose and plasma concentrations. Dosages ≤1800 mg/day were compared to those ≥1800 mg/day. Patient selection criteria excluded people with serious or unstable psychological conditions. There were no limitations on concurrent medications. The study population was 2216 patients.

73. As rated by the physician, seizure control was good or excellent in 66% of patients, but only 48% of patients met criteria required for evaluation of efficacy. Quality of life assessments for the evaluable population showed statistically significant improvement compared to baseline with gabapentin treatment. Adverse events in the ≤1800 mg/day group occurred at a higher incidence overall, probably due to the fact that patients with adverse events might not increase their dose or might withdraw from the study. Patient narratives in the Research Report were only provided for serious events.

74. As described in the following Tables, a total of 73 serious adverse events occurred, many of which were related to psychobiological function. Serious psychobiological adverse events included 5 reports of overdose, 3 reports each of depression and psychosis and 1 report each of the following events: suicide attempt (a completed suicide), anxiety, confusion, hostility, personality disorder, and thinking abnormal. The table below provides patient demographics for a subset of the serious psychobiological adverse events occurring during the STEPS trial.

75. Although there were 4 instances of suicidal behavior that occurred during the STEPS trial (as coded by PDG), only 1 was listed in the adverse event tables provided in the Research Report. In addition, one patient in the STEPS trial committed suicide. This patient is listed in the Research Report for the STEPS trial and is noted in the medical literature.[40]

[40] *See* Beran et al., 2001. Additional publications describing the STEPS trial are also provided (Morrell, 1999; Morrell et al., 2000).

Serious Psychobiological Events (STEPS Trial)
(From the patient narratives, there were four suicidal events rather than the one listed in the adverse events tables)

Patient	Demog	AE	Dose	Day	Related	History	Mgmt	Non AE Meds	Outcome
70163	46, Caucasian, female	**Suicide** (Fatal)	1800	15	Def not	Pseudolupus, no other details of event available	N/A	Nefazodone antidepressant	Fatal
17012	29, Caucasian, male	Drug Overdose, ***Attempted suicide***	900	14	Definitely	Astrocytoma	Interrupted	None listed	resolved
29324	29, Hispanic, female	Psychosis, chest wound- ***Suicide attempt (self inflicted stab wound to the chest)***	2700	73	Unlikely	Tubal ligation, C-section Narrative: Psychosis, siblings committed suicide	GBP cont.	None listed	resolved
23812	52, Hispanic, female	Psychosis, ***Suicidal***	1500	68	Unlikely	Depression Hypercholesterolemia Diabetes Dermatitis Narrative: Suicidal ideation, attempt	GBP cont., outpatient therapy	Nefazodone antidepressant	Not specifically stated
13775	34, Caucasian, male	Insulin **overdose** (fatal)	1800	28	Def not	Alcohol abuse and diabetes	NA probable cause unk.	Insulin	Fatal
33624	35, Caucasian, male	Drug abuse, phenobarbital **overdose**	3600	65	Def not	None listed	GBPdisc. W/D due to abusive behavior	None listed	resolved

Text in italics identifies a more fully descriptive narration.

Serious Psychobiological Events (STEPS Trial, *continued*)

Patient	Demog	AE	Dose	Day	Related	History	Mgmt	Non AE Meds	Outcome
27955	46, Black, female	Major **depression**	1500	37	Unlikely	Hysterectomy, Hypertension, Headache, Depression	GBP cont., Prozac for depression	Amytriptyline	resolved
101012	35, Caucasian, female	Major **depression**	1800	1	Unlikely	Major depression	ECT, W/D, but continued taking GBP	Benzodiazepines, barbiturates	Resolved
15254	40, Caucasian, female	Major **depression**	1800	111	Unknown	Chronic depression	GBP cont.	None listed	resolved
12692	47, Caucasian, male	**Aggressive**, destructive behavior	2400	63	Possibly	Paranoid schizophrenia Narrative: Aggression	Decr. To 900mg	Buspar Haldol Molindone-antipsychotics	resolved
12152	20, Hispanic, male	**Psychiatric** disorder, Behavioral disturbance	1800	36	unlikely	None listed Narrative: Depression	Interrupted	Imipramine Haldol	Resolved
28942	34, Caucasian, female	**Anxiety**	900	57	unlikely	Huntington's chorea Narrative: Anxiety	GBP cont., alprazolam for anxiety	Desipramine -TCA Sertraline-SSRI Trazodone Clonazepam	ongoing
29623	25, Black, female	**Psychotic** break	1200	10	Def not	Psychosis	GBP disc.	Lithium Prolixan (NSAID)	Ongoing

76. In terms of adverse events overall (serious and non-serious), there were 33 reports of depression, 9 reports of overdose, 1 suicide attempt, 3 reports each of psychosis and depersonalization. A total of 234 patients withdrew due to adverse events. Common adverse events leading to withdrawal were dizziness and somnolence. Psychobiological adverse events leading to patient withdrawal are provided below.

Psychobiological adverse events leading to withdrawal (STEPS trial):

Event	**≤1800mg**	**>1800-2400mg**	**>2400-3600mg**	**>3600mg**	**All**
# patients at this dose	*2216*	*781*	*719*	*12*	*2216*
Overdose	**2**		**1**		**3**
Suicide attempt	**1**				**1**
Agitation	1				1
Anxiety	5				5
Confusion	17				17
Delirium	1				1
Depression	6				6
Emotional lability	4				4
Hallucinations	1				1
Hostility	2				2
Manic reaction	1				1
Nervousness	6		1		7
Neurosis	1				1
Paranoid reaction	1				1
Personality disorder	3				3
Psychosis	1				1
Thinking abnormal	7				7

77. The table below lists all psychobiological adverse events in patients receiving gabapentin during the STEPS trial. Note that the total number of events (provided in the **All** column) does not match the combined number at each of the respective doses. It is unclear why this is, but it may relate to the fact that patients were titrated to different dosages (and thus may have experienced the same event at different dosage levels).

All Psychobiologic Adverse Events (STEPS Trial):

Event	≤1800mg	>1800-2400mg	>2400-3600mg	>3600mg	All
# patients at this dose	*2216*	*781*	*719*	*12*	*2216*
Overdose	**8**	**1**	**1**		**9**
Suicide attempt	**1**				**1**
Agitation	5	1	1		5
Anxiety	12	2	3		14
Confusion	37	5	4		41
Delirium	2				2
Depersonalization	2		1		3
Depression	25	8	10		33
Emotional lability	8	2	4		12
Euphoria	2		1		3
Hallucinations	5				5
Hostility	10	6	5		11
Manic reaction	1				1
Nervousness	27	8	12		34
Neurosis	1				1
Paranoid reaction	1				1
Personality disorder	12	1	1		12
Psychosis	2		1		3
Thinking abnormal	22	9	6		24

78. As set forth above, Neurontin adverse event data from both adult monotherapy and add-on trials were examined during the period encompassing January 1994 through September 1996. A number of adverse events related to psychobiologic function were observed including reports of suicide, suicide-related behavior, depression, intentional overdose, hostility and psychosis. The numerous psychobiologic adverse events experienced by epileptic patients during this period should have prompted further study by Pfizer Defendants to ascertain their association with gabapentin. In combination with the overdose and suicidal/depression events observed in the pre-FDA approval stage, these trends represent a signal that should have been acted upon. The necessary changes at this time should have included changes in the product labeling to adequately reflect the risk of these adverse psychobiologic effects and increased efforts to inform physicians of the possibility of these events in a population (epileptics) already at risk.

79. Specifically, enhanced information should have been provided in the label warning patients and prescribers about the risks of suicidal behaviors (suicidal ideation, suicidal thoughts) and in particular, suicide attempt. The inclusion of *suicide gesture* in the gabapentin label did not adequately reflect the significant number of suicide attempts observed in clinical trials sponsored by Pfizer Defendants to that point in time.[41] Furthermore, both references to suicide-related events in the labeling (suicidal, suicide gesture) are contained in the section describing events observed prior to marketing approval. Pfizer Defendants have yet to update the gabapentin labeling to reflect the significant number of suicide-related events (post-marketing reports) observed subsequent to the approval of gabapentin. Additional data sources, including the company's internal database and Annual Reports, Periodic Safety Update Reports and the Spontaneous Reporting System, confirmed these suicide-related events and provided further evidence that enhanced warnings were necessary to provide patients with complete information regarding the risks and benefits of gabapentin.

[41] Despite any assertion by Pfizer Defendants that a reader of their product label for Neurontin would understand "suicide gesture" to mean "suicide attempt", the term "suicide attempt" was in fact an unlabeled adverse drug experience because it was not listed in the product labeling. Indeed, to the physician reading the label, it was an "unexpected" adverse drug experience since it was not included in the product labeling. Yet, Pfizer Defendants were aware of such experiences and other psychobiologic adverse events not included in the labeling. *See* 21 CFR 314.80(a): "Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity." Because "suicide attempt' is a term more specific --- and arguably even of greater severity --- than "suicidal" or "suicidal gesture", it was an unlabeled, unexpected adverse drug experience. Noteworthy, in-house Pfizer Defendant documents referenced "suicide attempt" as a labeled event (incorrectly) even though they sought fit not to include the term on their actual product labeling. *See* Pfizer_CPacella_0050918 at 0050926, where Pfizer's Drug Safety Product Reference Guide (draft September 12, 2000) indicates "suicide gesture or suicide attempt (is serious)" as labeled adverse events. Such a circumstance reflects that Pfizer Defendants provided more detailed information within their own company than they chose to provide to those individuals actually using their product.

NEURONTIN PEDIATRIC EPILEPSY STUDIES

80. Neurontin pediatric studies reviewed for the time period 1994 – 1996 were ongoing as of the cutoff date for evaluation (September 1996). Despite this, there were a number of notable adverse events related to psychobiological function that occurred in pediatric patients, including one report of a patient being suicidal.[42] An overview of the top five psychobiological adverse events occurring in pediatric patients is provided below.

Psychobiological Adverse Events in Pediatric Trials

Studies[a]	***# Patients***[b]	***(# events)***	
Pediatric Studies (4)	661	Emotional Lability	41
		Hostility	22
		Nervousness	20
		Thinking Abnormal	16
		Confusion	8
		Anxiety	6
		Personality Disorder	3
		Depression	2
		Hallucinations	2
		Agitation	1
		Apathy	1
		Frustration	1
		Hysteria	1
		Psychiatric Disorder	1
		Psychosis	1
		Suicidal	**1**

[a] Studies initiated or ongoing during the observed time period (January 1994 through September 1996) were included in the analysis

[b] number of patients receiving at least one dose of gabapentin

81. In addition, there were 22 instances of positive dechallenge from a total of 16 patients participating in pediatric gabapentin trials. These included the patient who expressed a desire to kill himself (suicidal) as well as other events of emotional lability and hostility.

[42] *See* RR 720-04231 at p 425

CLINICAL STUDIES – EPILEPSY (PEDIATRIC – Ongoing Studies)

Study # (RR #)	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-086; 945-186 (720-03891)	A 12-Week, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Gabapentin as Add-On Therapy in Children with Refractory Partial Seizures (Protocol 945-86 and 945-186)	6-6-93 to 12-20-96	Hostility {***9***, ***one unrelated***}; Emotional Lability {***5***, ***two unrelated***}; Nervousness {2}; Personality Disorder {2}; Psychiatric Disorder {1}; Confusion {1}; Thinking Abnormal {1}; Agitation {1}
945-087; 945-187 (720-03893)	Report on an Open-Label Extension of a Double-Blind, Placebo-Controlled, Multicenter Study of Gabapentin (CI-945, Neurontin) as Add-On Therapy in Children with Partial Seizures (Protocol 945-87/187)	1-29-94 to 5-14-97	Emotional Lability {***12***, ***four unrelated***}; Hostility {***9***, ***two unrelated***}; Confusion {***7***, ***four unrelated***}; Nervousness {5}; Anxiety {1}; Apathy {1}; Thinking Abnormal {1}; Hallucination {***1***, ***unrelated***}
945-094 (720-04231)	Gabapentin Pediatric Monotherapy Trial: A Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study in Pediatric Patients with Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS) (Protocol 945-094)	8-17-94 to 1-13-98	Hostility {***3***, ***two unrelated***}; Emotional Lability {***9***, ***one unrelated***}; Personality Disorder {***1***, ***unrelated***}; Suicidal {***1***, ***unrelated***}; Nervousness {***8***, ***three unrelated***}; Thinking Abnormal {***3***, ***two unrelated***}; Anxiety {***2***, ***one unrelated***}
945-095 (720-04362)	An Extended Open-Label Gabapentin (CI-945) Pediatric Monotherapy Trial Following a Double-Blind Study (Protocol 945-094) in Pediatric Patients with Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS) (Protocol 945-095)	9-13-94 to 12-22-98	Emotional Lability {***15***, ***three unrelated***}; Thinking Abnormal {***11***, ***six unrelated***}; Hostility {***5***, ***three unrelated***}; Nervousness {***5***, ***two unrelated***}; Anxiety {***3***, ***all unrelated***}; Depression {***2***, ***both unrelated***}; Frustration {***1***, ***unrelated***}; Hallucination {***1***, ***unrelated***}; Hysteria {***1***, ***unrelated***}; Psychosis {***1***, ***unrelated***}

*Consistent with the convention used by Pfizer Defendants, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted.

NEURONTIN NON-EPILEPSY STUDIES

82. The safety and efficacy data from 4 non-epilepsy clinical trials initiated, but not completed during the period January 1994 through September 1996 are provided in this section. Three (3) of these trials were performed in patients with psychiatric indications (social phobia, panic disorder and bipolar disorder) and one (1) trial was performed in patients with diabetic peripheral neuropathy. Many of the adverse events observed in these trials were related to psychobiologic function. No instances of suicidal behavior were observed in these trials (*i.e.*, completed suicide, suicide attempt or suicidal ideation). There was one instance of a positive dechallenge involving a psychobiological adverse event (thinking abnormal) from the diabetic neuropathy trial (945-210). The five most common psychobiological adverse events in these trials (see Tables below) were nervousness, confusion, thinking abnormal, depersonalization and anxiety (4 events) and euphoria (4 events).

83. Results obtained in the social phobia trial suggested that gabapentin is an effective treatment for this condition. However, this finding was not replicated and Pfizer Defendants did not attempt to secure a label indication. **Effects of gabapentin were not different from placebo for both the panic disorder and bipolar disorder trials. Despite this, these indications were marketed and promoted.** Gabapentin was effective in alleviating painful symptoms associated with diabetic peripheral neuropathy and was marketed for this indication although it was never approved by FDA.

Overview of all Psychobiological Events (*continued*)

Studies[a]	***# Patients***[b]	***Psychobiological AE's (# events)***[c]	
CLINICAL NON-EPILEPSY STUDIES			
Bipolar Disorder (1)	58	Nervousness	12[c]
		Confusion	10
Social Phobia (1)	34	Thinking Abnormal	8
		Anxiety	4
Panic Disorder (1)	52	Depersonalization	5
		Euphoria	4
Peripheral Neuropathy (1)	84	Depression	2
		Manic Reaction	2
		Emotional Lability	1
		Manic Depressive Reaction	1
		Paranoia	1
		Personality Disorder	1
		Psychosis	1

[a] Studies initiated or ongoing during the observed time period (January 1994 through September 1996) were included in the analysis

[b] number of patients receiving at least one dose of gabapentin

[c] Psychobiological adverse events occurring in each of the 4 listed studies were pooled for this analysis.

CLINICAL STUDIES – NON-EPILEPSY TRIALS (Ongoing Studies)

Study #	Title	Trial dates	Psychobiologic Adverse Events* (Gabapentin)
945-203 (720-03850)	Treatment of Social Phobia with Gabapentin: A Placebo-Controlled Study	4-26-96 to 5-22-97	Nervousness {5}; Thinking Abnormal {4}; Anxiety {***2***, ***one unrelated***[#]}; Confusion {1}; Depersonalization {1}; Depression {1}; Euphoria {1}; Personality Disorder {1}
945-204 (720-03851)	A Placebo-Controlled Trial of Gabapentin in Patients with Panic Disorder	7-15-96 to 10-11-97	Depersonalization {3}; Nervousness {2}; Anxiety {***1***, ***unrelated***}; Confusion {1}; Depression {1}; Euphoria {1}; Thinking Abnormal {1}
945-209 (720-04174)	Gabapentin Adjunctive Treatment in Patients with Bipolar Disorder	3-96 to 7-97	Manic Reaction {***2, both unrelated***}; Manic Depressive Reaction {***1, unrelated***}; Confusion {***1, unrelated***}; Paranoia {***1, unrelated***}; Nervousness {1}; Psychosis {***1, unrelated***}
945-210 (720-03908)	A Double-Blind Placebo-Controlled Trial of Gabapentin for Treatment of Painful Diabetic Peripheral Neuropathy	7-2-96 to 3-20-97	Confusion {7}; Nervousness {***4, one unrelated***}; Thinking Abnormal {***3, one unrelated***}; Euphoria {2}; Anxiety {***1, unrelated***}; Depersonalization {1}; Emotional Liability {1}

*Consistent with the convention used by Pfizer, adverse events were considered related to gabapentin if coded as unknown, possibly, probably or definitely related; events considered unrelated are noted

84. As referenced above, Pfizer Defendants pursued a clinical trial regarding **Gabapentin Adjunctive Treatment in Patients with Bipolar Disorder** (720-04174). The trial dates encompassed March 1996 – July 1997. In these trials, patients were randomized to receive either gabapentin (n=58; 600-3600 mg/day) or placebo (n=59) for 10 weeks in this single-blind, flexible-dose, parallel group, multicenter study. Patients included in the study were diagnosed as having bipolar disorder (DSM-IV criteria) despite ongoing therapy with valproate, lithium, or a combination of the two drugs. The following conditions were excluded from the trial: delirium, dementia, amnesia, cognitive disorders, schizophrenia, substance dependence, anti-social personality disorder. Antidepressant use was not allowed.

85. The primary efficacy outcomes were the change in the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale. Numerous secondary endpoints of efficacy were measured including Percentage of Internal States Scales responders; Clinical Global Impression of Severity Score; Hamilton Anxiety Scale; Clinical Global Impression of Change and the SF36 Quality of Life Questionnaire.

86. Results from the trials demonstrated that **Gabapentin was not effective in treating bipolar disorder**. **Placebo, not gabapentin, showed a significant improvement in YMRS.** No significant differences were noted between the placebo and gabapentin groups for baseline to endpoint changes in the Young Mania Rating Scale and the Hamilton Depression Rating Scale. Similarly, no difference between the placebo and gabapentin groups was observed for any of the secondary efficacy parameters measured. The study reports that the results may have been biased as gabapentin serum levels indicated that some patients failed to take the study medication as directed.

87. Notwithstanding this clinical trial being completed in approximately 1997, results from this trial were not published (in the Journal of Bipolar Disorder) until 2000.[43] Despite Pfizer Defendants' knowledge as the lack of efficacy of Neurontin for this purported indication, there is no evidence that Pfizer Defendants via Dear Healthcare Professional letters ever sought to pro-actively communicate the results of this clinical trial to the population Pfizer Defendants knew or should have known were prescribing Neurontin for Bipolar Disorder. Conversely, where clinical trial results were favorable to Pfizer Defendants, it is apparent that such an educational campaign to healthcare professionals was pursued. For example, a review of documents reflects that Pfizer Defendants via the "Marketing" Department had Dear Healthcare Professional letters regarding treatment of Social Phobia with Neurontin.[44] The correspondence states in part:

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[43] *See* Pande AC, Crockatt JG, Janney CA et al., *Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group*. Bipolar Disord, 2: 249-255. *See* Deposition of Adrian Vega, June 13, 2007, at Exhibit 14. The aforementioned article was based upon Pfizer Defendants' Research Report 720-04174, issued March 26, 1999 and which covered clinical trial research from March '96 – July '97. *See* RR 720-04174; Deposition of Adrian Vega, June 13, 2007 at Exhibit 16.

[44] *See* WLC_CBU_000836. Pfizer Defendants' clinical trial regarding treatment of Social Phobia with Neurontin culminated in Atul Pande's publication of the following article: *Treatment of Social Phobia with Gabapentin: A Placebo Controlled Study*, Journal of Clinical Psychopharmacology, Vol. 19, No. 4 (1999). The results included Pande's assertion that treatment with gabapentin as compared to placebo significantly reduced symptoms of social phobia.

> As part of an educational service and at its expense, Parke-Davis, marketer of NEURONTIN, is providing healthcare professionals with a reprint of the article listed below. The article reports on a study of NEURONTIN for the treatment of social phobia. This information concerns a use that has not been approved by the Food and Drug Administration. There are products or treatments that have been approved for social phobia.[45]

In light of Pfizer Defendants' actions to distribute information favorable to marketing of Neurontin (*e.g.*, Social Phobia article), their inaction regarding the unfavorable information about Neurontin with Bipolar Disorder may have suppressed critically-important information.[46] Pfizer Defendants failed to reasonably warn healthcare professionals of Neurontin's lack of efficacy, particularly pertaining to "off-label" psychiatric uses. This failure to warn is alarming in light of Pfizer Defendants illegal promotional scheme for "off-label" uses, and even in the absence of a promotional scheme, Pfizer Defendants knew of the widescale use of Neurontin for "off-label" psychiatric uses and should have reasonably warned about its lack of efficacy.[47]

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[45] WLC_CBU_000836.

[46] Even in response to specific inquiries about mood disorders, Pfizer Defendants suppressed Pande's article reflecting lack of efficacy with Neurontin use in a bipolar disorder population. For example, Pfizer Defendants' witness, Adrian Vega, testified on June 13, 2007 that in response to specific inquiries from prescribers, Pfizer Defendants' Medical Communication (or Medical Information) Department provided Standard Response Documents. *See* Deposition of Adrian Vega, June 13, 2007. Pfizer Defendants' standard response document on mood disorders included a specific section entitled, "Bipolar Disorder". *See* Deposition of Adrian Vega, June 13, 2007, at Exhibit 15. However, the section did not specifically reference either Pande's article or the actual Research Report. Instead, there was merely a footnote (*i.e.*, number 17) indicating "Data on file, Parke-Davis" presumably referencing the subject research report on bipolar disorder. The section, "Bipolar Disorder" The section on "Bipolar Disorder" did however reference other favorable information regarding Neurontin (*e.g.*, "Gabapentin showed a positive response in most reports. The case reports of one to five patients did well on gabapentin for up to several months. . . .In the studies with larger numbers, at least half of the patients had a positive response…."). In a separate section, "Mania and Other Disorders", Pfizer Defendants did acknowledge a "double-blind placebo for which gabapentin was shown not be effective in bipolar was also not effective in controlling mania-related symptoms."

[47] *See* Bernstein, *Enhancing Drug Effectiveness and Efficacy through Personal Injury Litigation*, Journal of Law and Policy, at p. 148: "Lack of safety and lack of effectiveness both violate a popular, uncontroversial, established-for-decades statutory mandate..... True, the harm of an ineffective drug is harder to see than the harm of an unsafe one, and when harm is not seen, personal injury litigation appears beside the point. It is not. Safety and effectiveness are related conditions that cannot be understood in isolation from each other. Lack of effectiveness is central to lack of safety. Without the possibility of good results, even small risks become intolerable. Without alignment between label-promises and outcomes, the perils of deceit, wrongfully gained revenue, and emotional distress loom large. Without therapeutic benefit from a product ... a patient remains in danger. Lack of effectiveness in a drug causes plenty of harm. A subset of injured persons ought to find relief in the courts for this injury.".

88. All psychobiological adverse events observed in the Bipolar study are provided in the following Table.

All Psychobiological Adverse Events (Bipolar Study)

Event	Placebo	Gabapentin
Manic reaction	5	2
Manic depressive reaction	0	1
Confusion	2	1
Paranoia	0	1
Nervousness	0	1
Psychosis	0	1
Thinking abnormal	2	0

89. As referenced above, Pfizer Defendants pursued a clinical trial regarding Neurontin for use in treating Diabetic Peripheral Neuropathy, entitled **A Double-Blind Placebo-Controlled Trial of Gabapentin for Treatment of Painful Diabetic Peripheral Neuropathy** (945-210). The Trial dates encompassed July 2, 1996 through March 20, 1997.

90. In this placebo controlled trial, gabapentin was administered for pain relief in diabetic neuropathy for a total of 8 weeks. Patients were allowed the use of SSRIs, but no other antidepressant, anticonvulsants, pain medication, or neuroleptics (though one placebo patient did take amitriptyline, a tricyclic antidepressant). Patients with serious psychological conditions were excluded from the study. There were no patient listings of concurrent medication or prior medical history in the research report.

91. Gabapentin produced significantly greater pain relief compared to placebo treatment. Some aspects of the patient's quality of life (as assessed by the SF-36 Quality of Life Questionnaire and Profile of Mood States) were improved by gabapentin. These included Anger/Hostility; Total Mood Disturbance; and Mental Health. **More patients in the gabapentin group experienced an adverse event related to psychobiologic function** (see chart below). This study was published in JAMA in 1998 (Backonja et al.). Of 165 total patients, there were 7 withdrawals involving patients taking Gabapentin 900-3600 mg/day versus 5 patients taking placebo. Withdrawals due to psychobiological adverse events in patients taking Gabapentin included the following:

Thinking abnormal	1- 900mg/day GBP, positive de-challenge, possibly related, no history listed
Confusion	1- 2400mg/day GBP, positive de-challenge, probably related, no history listed

92. Psychobiologic Adverse Events observed during the Diabetic Neuropathy trial are set forth below.

Psychobiologic Adverse Events (Diabetic Neuropathy Trial)

Event	Placebo	Gabapentin
Confusion	1	7
Anxiety	1	1
Nervousness		4
Thinking abnormal		3
Euphoria		2
Depersonalization		1
Emotional lability		1

DEATHS, SERIOUS ADVERSE EVENTS AND CLINICAL STUDY WITHDRAWALS (1994-1996)

93. For the time period 1994-1996, data on study deaths, serious adverse events and withdrawals were examined. The table below is an integration of patients expressing serious adverse events while participating in research studies, patients experiencing medical-related withdrawals from these studies and on-study patient deaths. All event descriptions were provided by the clinical investigator. All serious adverse events and the subsets of serious psychobiologic events are tabulated for patients receiving Neurontin and other employed study medications. The following terms were used in defining the constellation of psychobiologic adverse events: agitation, hostility, aggression, irritability, anxiety, manic reaction, apathy, neurosis, confusion, nervousness, depersonalization, overdose, depression, personality disorder, emotional lability, psychosis, forgetfulness, suicidal behaviors, hallucination, thinking abnormal.

94. The studies in this table are grouped by the following designations: Epilepsy Monotherapy (Completed Studies), Epilepsy Monotherapy (Ongoing Study), Epilepsy Add-On Therapy (Completed Studies), Epilepsy (Pediatric-Ongoing Studies) and Non-Epilepsy Trials (Ongoing Studies) which include investigations with social phobia, panic disorder, bipolar disorder and peripheral neuropathy. In addition, the table includes reference to the page number in this Integrated Summary of Safety Report pertaining to individual study descriptions.

95. The serious adverse events and withdrawal columns include the number of participants experiencing individual psychobiologic events. The number of deaths in a study is followed by an asterisk indicating that death was not caused by a psychobiologic event. The only exception is Study 945-193; 945-200 (Study of Titration to Effectiveness and Profile of Safety/STEPS) which includes one completed suicide event.

96. Serious events, including serious psychobiologic were observed in all drug groups. Of the patients withdrawing from a study due to an adverse event, approximately twice as many gabapentin patients (compared to placebo patients) withdrew as a result of a clinically-related psychobiologic event (26% versus 14%). The percentage of patients who experienced serious psychobiologic adverse events (17.3% gabapentin patients versus 13.8% placebo patients) was approximately 25% greater in the gabapentin-treated group compared with the placebo-treated group. In several instances, Pfizer Defendants and its clinical investigators underestimated the number of suicide related events.

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
Epilepsy Monotherapy (Completed Studies)		**Overall**	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-077 / p36	Gabapentin	8	0	13	3 (nervousness, 2; depression, 1)	2*
	Placebo	2	1 (depersonalization)	18	2 (hostility, 1; depersonalization, 1)	
945-177 / p38	Gabapentin	13	0	16	0	0
	Placebo	2	0	21	0	0
945-082 / p40	Gabapentin	7	2 (confusion, 1; thinking abnormal, 1)	9	3 (apathy, depression, 1; confusion, 1; nervousness, frustration, 1)	0
945-083 / p42	Gabapentin	24	5 (hypomania, overdose,1; confusion,1; psychosis, 1; depression, suicidal, 1; agitation,1)	16	4 (thinking abnormal, 1; hypomania,1; hostility,1; depression, nervousness, hostility, 1)	3*
945-088 / p45	Gabapentin	1	1 (psychosis)	0	0	0

* No deaths due to psychobiologic adverse events.

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
Epilepsy Monotherapy (Completed Studies)		**Overall**	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-089 / p47	Gabapentin	5	1 (psychosis)	3	1 (confusion)	0
945-36 / p49	Gabapentin	5	1 (confusion)	3	1 (psychosis)	1*
Epilepsy Monotherapy (Ongoing Study)						
945-092 / p53	Gabapentin	16	3 (confusion,1; overdose, 2)	10	0	3*
	Placebo	20	2 (thinking abnormal, 1; confusion,1)	39	3 (confusion, 1; hallucination, 1; thinking abnormal, 1)	1*
Epilepsy Add-On Therapy (Completed Studies)						
945-090 / p60	Gabapentin	6	0	17	6 (confusion, 3; nervousness, 2;thinking abnormal, 1)	0
945-423 / p63	Gabapentin	7	1 (overdose)	4	2 (overdose,1; confusion,1)	1*

* No death(s) due to psychobiologic adverse events.

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
Epilepsy Add-On Therapy (Completed Studies)		**Overall**	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-430-004 / p65	Gabapentin	10	3 (forgetfulness, aggression, 1; anxiety,1; forgetfulness, depression, 1)	1	0	0
	Placebo	8	2 (irritability,1; depression, agitation,1)	4	2 (irritability,1; depression,1)	0
945-436-002 / p67	Gabapentin	2	0	UNK	UNK	0
	Placebo	1	0	UNK	UNK	0
945-462 / p69	Gabapentin	38	8 (forgetfulness, 8)	UNK	UNK	UNK
877-210G / p70	Gabapentin	7	1 (depression)	4	1 (anxiety; agitation,1)	1*
	Placebo	14	2 (emotional lability,1; psychosis,1)	6	1 (emotional lability)	0

*No death(s) due to psychobiologic adverse events.

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
Epilepsy Add-On Therapy (Completed Studies)		**Overall**	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-193; 945-200 / p72	Gabapentin	73	12 (anxiety, 1; confusion, 2; depression,3; hostility,1; personality disorder, 1;psychosis,3; thinking abnormal,1)	234	56 (agitation,1;anxiety,5;confusion,17 ;depression,6;emotional lability, 4;hallucinations,1;hostility, 2;manic reaction,1; nervousness,7;neurosis,1; personality disorder,3; psychosis,1; thinking abnormal,7)	**11 (*1 death due to suicide*)**
945-430003 / p77	Gabapentin	0	0	5	2; (Confusion, 1; drunk feeling, 1)	0
	Sodium Valproate	0	0	2	1 (Poor concentration)	0

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Epilepsy (Pediatric-Ongoing Studies)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
		Overall	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-086; 945-186 / p82	Gabapentin	9	0	6	3 (thinking abnormal, agitation, hostility,1;hostility,1;personality disorder,1;	0
	Placebo	3	0	3	1 (emotional lability)	0
945-087; 945-187 / p84	Gabapentin	14	3 (confusion,2; hostility,1)	13	8 (emotional lability,1;thinking abnormal,1;anxiety,apathy, nervousness,1;personality disorder,hostility,1;confusion,1; emotional lability,1; hostility,1;confusion,1)	0

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Epilepsy (Pediatric-Ongoing Studies)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
945-094 / p86	Gabapentin	6	2 (suicidal ideation,hostility, 1;overdose,1)	4	3 (emotional lability,1; emotional lability,thinking abnormal,1; emotional lability,1;	0
	Placebo	1	1 (overdose,1)	0	0	0
945-095 / p88	Gabapentin	10	2 (overdose,1; emotional lability,1)	6	3 (emotional lability,1;forgetfulness, emotional lability,1;hostility,1)	0

*No deaths due to psychobiologic adverse events.

Neurontin Summary of Adverse Events: Serious/Withdrawals/Deaths (*continued*)						
Study/ Reference Page	**Study Medication**	**Serious Adverse Events**		**Withdrawals**		**Deaths**
Non-Epilepsy Trials (Ongoing Studies		**Overall**	**Pyschobiologic**	**Overall**	**Pyschobiologic**	
945-203 / p93 **(Social Phobia)**	Gabapentin	0	0	6	4 (nervousness,1; thinking abnormal, 2;anxiety,1)	0
	Placebo	0	0	3	2 (nervousness,1;thinking abnormal,1)	0
945-204 / p96 **(Panic Disorder)**	Gabapentin	1	0	8	0	0
	Placebo	0	0	4	0	0
945-209 / p98 **(Bipolar Disorder)**	Gabapentin	6	2 (manic depressive reaction, 1; psychosis, 1)	7	3 (manic reaction, 2; manic depressive reaction, 1)	0
	Placebo	5	1(thinking abnormal)	5	4 (manic reaction, 4)	0
945-210 / p100 **(Diabetic Neuropathy)**	Gabapentin	3	0	7	2 (thinking abnormal, 1; confusion, 1)	0
	Placebo	2	0	5	0	0

ADVERSE EVENT DATA FROM OTHER SOURCES
1994-1996

97. This review includes events obtained from clinical research reports, regulatory reporting domestic assignments and international post marketing surveillance databases. This assembly of reports should have been emphasized by Pfizer Defendants in their routine investigations for pharmacovigilance directed to new events or changes in the frequencies and severities of previously reported events

98. Data pertaining to all psychobiological adverse event reports from clinical studies and post-marketing surveillance databases were examined. Numerous documents were reviewed to determine the reporting of adverse events, including suicide and suicide-related behaviors, during the period January 1994 through September 1996. These sources include the following: Research Reports; Annual Reports; Periodic Safety Update Reports; Pfizer's Internal Database of Postmarketing Adverse Events; FDA: Spontaneous Reporting System (SRS); and World Health Organization (WHO).

99. It is clear that similar psychobiological concerns were evidenced across the data sources. This uniformity should have triggered Pfizer Defendants to carefully assess and report these signals. For example, suicide and overdose related terms were reported in multiple databases. More suicide attempts than those reported by Pfizer Defendants were observed; in addition, attempted homicide reports in Neurontin treated patients were also observed. Similar groupings of psychobiological adverse events were also reported. For example, nervousness, confusion, depression, depersonalization, thinking abnormal, psychosis, emotional lability, agitation, aggression, hostility, and personality disorders were frequently evidenced in the clinical research reports.

100. There also appear to be relevant time-related trends in each of the surveillance databases. For example, depersonalization reports in the US Annual Report increased significantly in the first three quarters of 1996. It is possible that these events may be linked with the significant off-label use of Neurontin for psychiatric indications. As noted earlier, depersonalization has been linked with suicide-related issues. As such, these data should have raised clear safety concerns with respect to Neurontin use in patients predisposed to self-harm (such as patients with bipolar depression or psychotic episodes). Unfortunately, Pfizer Defendants did not amplify the labeling to reflect these events and prescribers and patients remained unaware of these potential risks.

101. Pfizer Defendants' Internal Database indicated that suicide ideation and/or intentional overdose were consistently in the top 10 reported serious psychobiological events and in the top 25 of all reported adverse events. The FDA Spontaneous Reporting System Database also provided signals of increased numbers of deaths, suicide attempts, overdose, psychotic disorder and others.

102. These databases collectively highlighted the growing safety concerns associated with gabapentin. It is difficult to understand Pfizer Defendants' continued use of the launch insert as these serious and potentially life-threatening events continued to grow.

103. The tables below provide an overview of adverse events related to suicide behavior as they were reported in various databases, Research Reports or annual reports as well as patient demographics from these events. The other reported psychobiologic events were reviewed previously in this report.

Suicidal / Homicidal / Overdose Events - from Research Reports

The *italicized* text in the tables below identifies the adverse event as it should have been coded.

Trial	Patient	Demog	AE	Dose	Day	Related	History	Mgmt	Outcome
945-193, 200	70163	46, female	Committed Suicide* (12/23/95)	1800	15	Definitely not	Pseudolupus	N/A	Death
945-193, 200	29324	29, female	Psychosis, chest wound (1/31/96); *Suicide attempt*	2700	73, 76	unlikely	Psychosis	No change	Recovered
945-193, 200	17012	29, male	Drug overdose (5/12/95) *Suicide attempt*	900	14	definitely	Not stated	Drug interrupted	Recovered
945-193, 200	23812	52, female	Psychosis*, (9/19/95) *Suicidal*	1500	68	unlikely	Psychosis; suicide attempts	No change	Not stated
945-083	9-17	18, male	Suicidal; *Suicide attempt*	3600	89	Definitely not	Not stated	No change	Recovered
945-083	7-10	47, female	Overdose; *Suicide attempt*	2400	258	Possibly	Depression	Discontinued	Recovered
945-094	2-11	10, male	Suicidal, Hostility	1800	84,85	Definitely Not	Aggressive behavior, hyperactivity	Drug interrupted	Recovered With sequelae
945-083	21-12	37, male	Hostility – patient shot 2 people	4800	246	Unlikely	Not stated	Discontinued	1 death

*Patients were on an antidepressant (Nefazadone)

104. Certain psychobiological adverse events should have been coded to disclose suicidal behavior. The specific narratives from these five (5) patients are set forth below:

Investigator Number: 2932
Patient Number: 29324
Adverse Event: PSYCHOSIS
CHEST WOUND

Patient no. 29324, a 29-year-old Hispanic female, experienced a period of psychosis and a stab wound to the chest while receiving 2700 mg/day of study drug. The psychotic episode began on study day 73 and the self-inflicted stab wound to the chest occurred on study day 76 (Study Day 1 was 16/11/95). Both events were considered to be severe in intensity with the psychosis lasting for 9 days and the stab wound for 21 days. The investigator considered the events to be unlikely related to study drug, however, the patient has a history of psychosis. The investigator considered the psychosis to be life-threatening, and the patient was hospitalized for the chest wound. These events have resolved with no change in the study drug dosing regimen.

The patient was admitted to hospital on 30 January 1996 with a self-inflicted stab wound to the chest. The patient has a history of psychosis in her family. A brother and sister were both diagnosed as psychotic and both committed suicide. The patient's mother has a history of paranoid ideation. The patient was observed in the hospital between 30 January 1996 and 5 February 1996. AED levels were found to be low due to patient's non-compliance. The adverse event is determined to be unlikely related to study drug. No dosage interruption was noted. The patient was released on 5 February 96 and scheduled for follow-up visits.

Investigator Number: 1701
Patient Number: 17012
Adverse Event: DRUG OVERDOSE

Patient no. 17012, a 29-year-old Caucasian male attempted suicide by overdosing on divalproex sodium (Depakote) and study drug while receiving 900 mg/day of study drug. It was considered to be moderate in intensity and lasted for 24 hours. The event began on study day 14 (Study Day 1 was 28/04/95). The investigator considered the event to be definitely related to study drug. The event was considered serious because the patient was hospitalized. The event resolved. Study drug was interrupted due to this event.

Investigator Number: 2381
Patient Number: 23812
Adverse Event: PSYCHOSIS

Patient no. 23812, a 52-year-old Hispanic female, experienced an episode of psychosis while receiving 1500 mg/day of study drug. The event began on study day 68 (Study Day 1 was 14/07/95). It was considered to be moderate in intensity and lasted for 10 days. The investigator considered the event to be unlikely related to study drug. The event was considered serious because the patient was hospitalized. There was no change in the study drug dosing regimen.

The patient presented for psychiatric admission to the Emergency Room on 19 September 1995. She was hearing voices telling her to kill herself and she feared for her life. She has a history of suicidal ideation. She first tried to kill herself when she was nine years old. Her mother and paternal aunt also have psychiatric histories (mother has schizophrenia). Immediate precipitating factors included the recent death of her aunt and uncle, family problems, and her failure to take her nefazodone. The investigator does not feel the episode was related to study drug.

The patient was released on 29 September 1995. She is being followed up by her primary care physician and is attending an outpatient psychiatric program.

Patient 9 (Study 945-83, Center 17), an 18-year-old male with epilepsy, was hospitalized in the psychiatric ward for situational depression and attempted suicide on Day 89. The patient had been receiving a dosage of 3600 mg/day gabapentin for the preceding 12 days. The patient was also receiving carbamazepine 600 mg/day. The patient had an argument with his father, got angry and jumped off a third floor balcony. He sustained two sprained ankles and hurt his neck. The patient was hospitalized for observation, recovered from the depression on Day 93, and was discharged on Day 115. The investigator considered these events moderate in intensity and definitely not related to study medication.

Patient 7 (Study 945-83, Center 10), a 47-year-old white woman with epilepsy and a history of depression, developed hypomania on Day 254 of gabapentin treatment; the patient had been receiving a dose of 3300 mg/day gabapentin for the previous 32 days. The patient was also receiving 300 mg/day phenytoin. As a result of the hypomania, gabapentin dosage was reduced to 2400 mg/day on Day 256. On Day 258 the patient ingested about 50 capsules of gabapentin (15,000 mg), and was hospitalized. The patient recovered from the overdose and was discharged on Day 262. Hypomania continued, and gabapentin was discontinued as a result, with the last dose taken on Day 285. Hypomania resolved on Day 287. The investigator considered the hypomania and overdose moderate and possibly related to gabapentin.

NEURONTIN ANNUAL REPORTS

105. As provided in the following Tables, psychobiological adverse events from quarterly and annual reports prepared by Pfizer Defendants were analyzed. These reports encompass the time period from January 1, 1994 through September 30, 1996 and include both serious and non-serious reports. There are only 2 reports of suicide in their database from 1994 and none in the years 1995 and 1996. Similarly, there are only 2 reports each for suicidal ideation and suicide attempt during the years 1994 through 1996. The database does list 13 cases of overdose; however, it is not known whether these events represent intentional overdoses (*i.e.*, a suicide attempt) or simply a dosing error (unintentional overdose). Importantly, the table below demonstrates the large increase in hostility, confusion and nervousness events between 1994 and 1995 and also the large jump in the number of events of depersonalization between 1995 and 1996. All of these events should have precipitated action on the part of Pfizer Defendants to re-examine the adequacy of the gabapentin product label.

Adverse Events Found in Annual Reports Prepared by Pfizer Defendants (1994 – 1996)

	1994					1995					1996			
Adverse Event	**Q1**	**Q2**	**Q3**	**Q4**	**1994 total**	**Q1**	**Q2**	**Q3**	**Q4**	**1995 total**	**Q1**	**Q2**	**Q3**	**1996 total**
Death*	1	5	11	13	**30**	10	9	4	3	**26**	3	3	4	**10**
Reaction Aggravated	1	5	14	6	**26**	11	10	1		**22**			2	**2**
Hostility		7	3	3	**13**	6	9	6	4	**25**	6	3	6	**15**
Aggression/ Aggressive		7	2	4	**13**	4	5	2		**11**				
Agitation		1	3	4	**8**	3		1	2	**3**	1	3	3	**7**
Anxiety		2	1	5	**8**	1	1			**2**		1	4	**5**
Depression		1	1	5	**7**			2	3	**5**	1	2	5	**8**
Overdose		2	2		**4**		1	2	1	**4**	3	1	1	**5**
Confusion		2	1	1	**4**	4	6	1	4	**15**	4	4	1	**9**
Personality Disorder			2	3	**5**				3	**3**	7	4	4	**15**
Nervousness	1	1	1		**3**	2	7	1	2	**12**	6	4	4	**14**
Psychotic[&]			1	2	**3**	2			2	**4**			1	**1**
Depersonalization	1	1			**2**		1			**1**	6	3	4	**13**
Thinking Abnormal		1		1	**2**		3	1	3	**7**	4	2	1	**7**

*Death and Sudden Death adverse event terms were merged

Adverse Events Found in Annual Reports Prepared by Pfizer Defendants (1994 – 1996, *continued*)

	1994					1995					1996			
Adverse Event	**Q1**	**Q2**	**Q3**	**Q4**	**1994 total**	**Q1**	**Q2**	**Q3**	**Q4**	**1995 total**	**Q1**	**Q2**	**Q3**	**1996 total**
Suicide			1	1	**2**									
Suicidal Ideation	1	1			**2**									
Suicide Attempt		1			**1**			1		**1**				
Hallucinations							1		1	**2**		2	1	**3**
Emotional Lability							1	1		**2**	1	2	1	**4**
Abnormal Dreams											2	3		**5**

[&] Psychotic and Psychosis adverse event terms were merged

106. Psychobiological adverse events (including suicide-related behaviors) related to gabapentin and reported in Periodic Safety Update Reports (PSURs) prepared by Pfizer Defendants were reviewed. For the time period 1994-1996, a total of 3 PSUR documents were reviewed, each of which is discussed separately below. For each of the PSUR documents, an overview of suicidal and overdose events contained in the respective PSUR documents is provided. This is followed by an overview of all psychobiological adverse events. Two of the PSUR documents reviewed for this time period encompass time periods outside of the imposed range (*i.e.*, the 1st PSUR starts in April 1993 and the 3rd PSUR contains data through December 1996). Thus, it is possible that some of the noted adverse events may have occurred outside of the designated time period (January 1994 through September 1996).

1st Periodic Safety Update Report

Period Covered: April 1, 1993 through February 22, 1995;

Includes 625 events from the United Kingdom and the United States

107. Three cases of either suicide or suicidal tendencies are mentioned and one patient committed suicide. **One adverse event coded as self injury may have been a suicide attempt (044-0945-940033-00)**. Limited information was provided for the suicide/suicidal cases. The 1st PSUR (Europe) also mentions 12 cases of overdose (not all of the cases were included in the line listing of events) and also notes a publication by Garafalo et al., discussing 5 cases of gabapentin overdose. The overdose cases were not examined in detail, apparently because most reports contained no "…*evaluable information*".[48] Relevant events related to suicide behavior or overdose are provided in the table below. The conclusion from this PSUR document stated that no new specific or particular risk was associated with gabapentin therapy.[49]

[48] *See* Pfizer_PSUR_0002015-0002193 at 0002049
[49] *See* Pfizer_PSUR_0002015-0002193 at 0002058

Listing of Suicide/Suicidal/Overdose Events from the 1st PSUR

Code	Country, Demog	AE	Dose	Related?	Outcome
044-0945-940033-00	UK 26 y/o M	Suicide attempt* (self injury)	1200 mg	Possible	Recovered
044-0945-940016-01	UK 27 y/o M	Suicidal tendency	300 mg	Possible	Recovered
001-0945-940170-01	USA 25 y/o F	Overdose (unknown if intentional)	7500 mg	Possible	Unknown
001-0945-940103-00	USA 10 y/o M	Overdose; Suicide attempt	(10.5 g)	Possible	Unknown
001-0945-940080-00	USA 19 y/o	Overdose (unknown if intentional)	Not given	Possible	Unknown
001-0945-940300-02	USA 30 y/o F	Suicide	1800 mg	Unlikely	Death

*** This event was coded as agitated, violent, self injury**

108. All psychobiological adverse events from the 1st PSUR (April 1993 to May 1995) were reviewed. A more general examination of psychobiological adverse events associated with gabapentin therapy reveals a number of events which should have signaled concern by the Pfizer Defendants. Despite reports of myriad adverse events related to psychobiological function, Pfizer Defendants chose to ignore these events. A more careful examination of these events should have been undertaken and subsequently, changes to the product labeling should have been affected to reflect the rate and severity of these events.

Psychobiological Adverse Events from the 1st Neurontin PSUR

ALL PSYCHOBIOLOGICAL ADVERSE EVENTS	# EVENTS
Abnormal Behavior	5
Acutely Anxious	1
Affective Disorder	1
Agitation	11 (1)
Aggression	2
Confusion	4 (1)
Delusion	1
Depression	1
Detached/ Spaced Out	1
Hallucinations	4
Irritability	2
Mood Changes	3 (1)
Overdose	3 (3)
Paranoia	7 (1)
Personality Changes	1
Psychosis	8 (2)
Psychotic	5 (1)
Self-Injury	1
Severe Anxiety	2
Suicide Attempt	1 (1)
Suicidal Tendency	1
Thinking Abnormal	1 (1)
Violent	1
() = United States cases	

2nd Periodic Safety Update Report

Period Covered: February 22, 1995 through December 31, 1995

109. Psychobiological adverse events reported in Defendants' second PSUR were reviewed. **No new information related to suicide or overdose events was found in this document.** This document did note a completed suicide in a patient overdosing on multiple antiepileptic drugs. This is likely the same patient noted in the 1st PSUR (note that there is overlap between the 1st and 2nd PSUR documents). Of note, this document did provide a report by Dr. Michael Trimble entitled "Psychosis with Gabapentin", which reviews 6 adverse event reports of psychosis associated with gabapentin (see below). In addition, the Trimble report discusses a case report published in the British Journal of Psychiatry (Short and Cooke, 1995) which describes hypomania associated with gabapentin therapy.

110. As there is a 3 month overlap between the 1st and 2nd PSUR documents, some of the psychobiological adverse events listed below may have been reported previously. As this document provided events occurring during a 10 month period only, there are fewer adverse events related to psychobiologic function.

Psychobiological Adverse Events from the 2nd Neurontin PSUR

February 1995 to December 1995

PSYCHOBIOLOGICAL ADVERSE EVENTS	# OF EVENTS
Abnormal Behavior	1
Agitation	3 (2)
Bizarre Behavior	2
Confusion	1 (1)
Hallucinations	5 (2)
Irritability	1
Mental Depression	1 (1)
Mood Changes	1 (1)
Psychosis	3 (2)
Psychotic Behavior (1)	11
Rage	2(2)
() = United States cases	

3rd Periodic Safety Update Report

Period Covered: January 1, 1996 through December 31, 1996

111. In the 3rd PSUR, there is 1 postmarketing report of a patient experiencing a self-inflicted stab wound to the chest. This event likely corresponds to the patient from the STEPS trial. In the Research Report for the STEPS trial, this event was coded as *Psychosis, Chest Wound*. No narrative was provided in the PSUR for this patient. This event should have been considered a suicide attempt and discussed within both the Research Report and the PSUR. The fact that this event was not further reviewed represents additional evidence that Pfizer Defendants chose to ignore these serious adverse events related to psychobiologic function.

112. A case of suicide ideation was also reported in the 3rd PSUR, along with multiple cases of drug overdose. The overdoses were not discussed in detail; thus it is unclear if they represent an intentional (suicide attempt) or unintentional (dosing error) event. The events are set forth in the Table below.

Suicidal/Overdose Events from the 3rd PSUR

Code	Country	AE	Dose	Related?	Outcome
001-0945-960051	USA	Overdose	Not given	Not related	UNK
001-0945-960387	USA	Overdose	Not given	Not related	recovered
031-0945-960002	Netherlands	Overdose	Not given	Related	recovered
036-0945-960003	Hungary	Overdose	Not given	Related	recovered
064-0945-960001	New Zealand	Overdose	Not given	Related	recovered
001-0945-960247	USA	Suicide ideation; explosive aggressive behavior	Not given	Not related	Recovered; Not recovered
001-0945-960096	USA	Suicide attempt; (Self-inflicted stab wound)	Not given	Not related	recovered

113. All psychobiologic adverse events reported in Pfizer Defendants' 3rd Periodic Safety Update Report were examined and are set forth in the Table below.

Psychobiologic Adverse Events in the 3rd PSUR

(January 1996 to December 1996)

PSYCHOBIOLOGICAL ADVERSE EVENTS	# OF EVENTS
Abnormal Behavior	13 (9)
Accidental OD	3 (3)
Agitation	9 (6)
Aggressive Behavior	19 (8)
Anxiety	9 (5)
Combative	1 (1)
Confusion	13 (7)
Delirium	1 (1)
Depersonalization	2 (1)
Depression	14 (11)
Feeling High	1 (1)
Forgetfulness	1
Frustration	1 (1)
Hallucinations	9 (5)
Hostility	5 (5)
Irritable	9 (5)
Manic Depression	2 (1)
Mood Swings	3 (2)
Nervousness	1 (1)
Neurosis	1 (1)
Overdose	5
Paranoia	1
Paranoid Ideation	1
Personality Changes	1 (1)
Personality Disorder	1
Post-ictal Psychosis	7 (6)
Psychotic	3(2)
Self-Abusing Behavior	1 (1)
"Spaced- out"	1 (1)
Suicide Attempt	1 (1)
Suicide Ideation	1 (1)
Verbally Abusive	1 (1)
Violent Behavior	1 (1)
Withdrawn	1
() = United States cases	

PARKE-DAVIS (PFIZER) INTERNAL PHARMACOVIGILANCE DATABASE

114. Cumulative adverse events contained in the Parke-Davis (Pfizer) internal database during the period covering January 1994 through September 1996 were reviewed. For the purposes of this time period, serious psychobiological adverse events were examined using the Preferred Term to clearly specify the reported events.

115. The tables provided on the following pages provide the number of cumulative events for each psychobiological adverse event (in descending order) for 1994, 1995 and 1996 (Q1, Q2, Q3). Interestingly, depression was the leading psychobiologic event reported in all three years and accounted for 3% of the overall database. Psychotic disorder reports were the second most frequently reported event every year (~2.5%). Suicidal ideation and overdose were always among the top 10 reported psychobiological events.

116. Multiple psychobiologic events were consistently found in the provided listing of the top 25 serious event reports across all body systems. Of specific concern, suicidal ideations and/or intentional overdose are included in the top 25 list each year. Collectively, the contribution of these events should have represented a clear signal to Pfizer Defendants, which should have then resulted in changes to the product label. This was especially critical given their focus on lucrative psychiatric off-label uses.

Cumulative Serious Psychobiological Events Reported to Pfizer Defendants' Internal Database (1994)

	Through 1994 Q4	
Term	**Reports**	**Pct***
Depression	13	3.16%
Psychotic Disorder	11	2.68%
Overdose	8	1.95%
Confusional State	7	1.70%
Suicidal ideation	6	1.46%
Hallucination	5	1.22%
Aggression	3	0.73%
Agitation	3	0.73%
Anxiety	3	0.73%
Intentional overdose	3	0.73%
Paranoia	3	0.73%
Delirium	1	0.24%
Delusion	1	0.24%
Depressed level of consciousness	1	0.24%
Hallucinations, mixed	1	0.24%
Hostility	1	0.24%
Hypomania	1	0.24%
Personality change	1	0.24%
Suicide attempt	1	0.24%

* Percentage of total serious adverse events across all body systems

Cumulative Serious Psychobiological Events Reported to Pfizer Defendants' Internal Database (1995)

	Through 1995 Q4	
Term	**Reports**	**Pct***
Depression	20	3.01%
Psychotic Disorder	17	2.56%
Confusional State	12	1.81%
Agitation	11	1.66%
Overdose	9	1.36%
Aggression	8	1.20%
Intentional overdose	8	1.20%
Suicidal ideation	7	1.05%
Hallucination	6	0.90%
Anxiety	4	0.60%
Suicide attempt	4	0.60%
Paranoia	3	0.45%
Delirium	2	0.30%
Delusion	2	0.30%
Depressed level of consciousness	2	0.30%
Anger	1	0.15%
Emotional distress	1	0.15%
Hallucination, auditory	1	0.15%
Hallucinations, mixed	1	0.15%
Hostility	1	0.15%
Hypomania	1	0.15%
Mood altered	1	0.15%
Personality change	1	0.15%
Personality disorder	1	0.15%

* Percentage of total serious adverse events across all body systems

Cumulative Serious Psychobiological Events Reported to Pfizer's Internal Database (1996)

	Through 1996 Q3	
Term	**Reports**	**Pct***
Depression	25	2.85%
Psychotic Disorder	21	2.40%
Confusional State	17	1.94%
Aggression	16	1.83%
Intentional overdose	14	1.60%
Agitation	13	1.48%
Overdose	9	1.03%
Anxiety	7	0.80%
Hallucination	7	0.80%
Suicidal ideation	7	0.80%
Suicide attempt	5	0.57%
Paranoia	4	0.46%
Delirium	3	0.34%
Personality disorder	3	0.34%
Anger	2	0.23%
Delusion	2	0.23%
Depressed level of consciousness	2	0.23%
Major depression	2	0.23%
Mood swings	2	0.23%
Emotional distress	1	0.11%
Hallucination, auditory	1	0.11%
Hallucinations, mixed	1	0.11%
Hostility	1	0.11%
Hypomania	1	0.11%
Intentional self-injury	1	0.11%
Irritability	1	0.11%
Mood altered	1	0.11%
Personality change	1	0.11%

* Percentage of total serious adverse events across all body systems

Top 25 Adverse Events Reported to Pfizer's Internal Database (1994 – 1996)

Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct
Convulsion	1994-Q4	73	17.76%	Convulsion	1995-Q4	118	17.77%	Convulsion	1996-Q2	148	18.66%
Status epilepticus	1994-Q4	32	7.79%	Death	1995-Q4	47	7.08%	Death	1996-Q2	48	6.05%
Death	1994-Q4	27	6.57%	Status epilepticus	1995-Q4	40	6.02%	Status epilepticus	1996-Q2	44	5.55%
Depression	1994-Q4	13	3.16%	Depression	1995-Q4	20	3.01%	Somnolence	1996-Q2	28	3.53%
Ataxia	1994-Q4	12	2.92%	Somnolence	1995-Q4	20	3.01%	Ataxia	1996-Q2	23	2.90%
Psychotic disorder	1994-Q4	11	2.68%	Grand mal convulsion	1995-Q4	19	2.86%	Depression	1996-Q2	22	2.77%
Grand mal convulsion	1994-Q4	10	2.43%	Ataxia	1995-Q4	19	2.86%	Pneumonia	1996-Q2	21	2.65%
Pneumonia	1994-Q4	10	2.43%	Psychotic disorder	1995-Q4	17	2.56%	Grand mal convulsion	1996-Q2	21	2.65%
Overdose	1994-Q4	8	1.95%	Pneumonia	1995-Q4	16	2.41%	Psychotic disorder	1996-Q2	19	2.40%
Somnolence	1994-Q4	8	1.95%	Sudden death	1995-Q4	12	1.81%	Confusional state	1996-Q2	16	2.02%

Top 25 Adverse Events Reported to Pfizer's Internal Database (1994 – 1996, *continued*)

Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct
Drug interaction	1994-Q4	8	1.95%	Confusional state	1995-Q4	12	1.81%	Dizziness	1996-Q2	16	2.02%
Confusional state	1994-Q4	7	1.70%	Pyrexia	1995-Q4	11	1.66%	Drug interaction	1996-Q2	15	1.89%
Lethargy	1994-Q4	6	1.46%	Agitation	1995-Q4	11	1.66%	Sudden death	1996-Q2	15	1.89%
Condition aggravated	1994-Q4	6	1.46%	Drug interaction	1995-Q4	11	1.66%	Pyrexia	1996-Q2	15	1.89%
Suicidal ideation	1994-Q4	6	1.46%	Lethargy	1995-Q4	10	1.51%	Vomiting	1996-Q2	14	1.77%
Pyrexia	1994-Q4	6	1.46%	Fall	1995-Q4	10	1.51%	Agitation	1996-Q2	12	1.51%
Thrombocythaemia	1994-Q4	5	1.22%	Overdose	1995-Q4	9	1.36%	Anticonvulsant drug level increased	1996-Q2	12	1.51%
Sudden death	1994-Q4	5	1.22%	Abdominal pain	1995-Q4	9	1.36%	Fall	1996-Q2	12	1.51%
Pneumonia aspiration	1994-Q4	5	1.22%	Dizziness	1995-Q4	9	1.36%	Lethargy	1996-Q2	11	1.39%

Top 25 Adverse Events Reported to Pfizer's Internal Database (1994 – 1996, *continued*)

Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct	Term	Date	Cumulative Reports	Pct
Neutropenia	1994-Q4	5	1.22%	Cerebrovascular accident	1995-Q4	9	1.36%	Intentional overdose	1996-Q2	11	1.39%
Diarrhea	1994-Q4	5	1.22%	Aggression	1995-Q4	8	1.20%	Aggression	1996-Q2	10	1.26%
Hallucination	1994-Q4	5	1.22%	Intentional overdose	1995-Q4	8	1.20%	Abdominal pain	1996-Q2	10	1.26%
Leukopenia	1994-Q4	5	1.22%	Condition aggravated	1995-Q4	7	1.05%	Headache	1996-Q2	9	1.13%
Abdominal pain	1994-Q4	5	1.22%	Weight increased	1995-Q4	7	1.05%	Overdose	1996-Q2	9	1.13%
Weight increased	1994-Q4	4	0.97%	Epilepsy	1995-Q4	7	1.05%	Tremor	1996-Q2	9	1.13%
Appendicitis	1994-Q4	4	0.97%	Suicidal ideation	1995-Q4	7	1.05%	Cerebrovascular accident	1996-Q2	9	1.13%
Tremor	1994-Q4	4	0.97%	Diarrhoea	1995-Q4	7	1.05%	Weight increased	1996-Q2	9	1.13%
Arthralgia	1994-Q4	4	0.97%	Pancreatitis	1995-Q4	7	1.05%				
Nausea	1994-Q4	4	0.97%								
Pancreatitis	1994-Q4	4	0.97%								
Ankle fracture	1994-Q4	4	0.97%								

117. Psychobiological adverse events reported to the Spontaneous Reporting System (SRS) Database during the period from January 1994 through September 1996 were examined. Of note, the numbers for several of these events, including deaths, suicide attempts and overdose, increased by a factor of 2 (or more) between 1994 and 1996. These trends should have served as a signal to Pfizer Defendants, prompting an immediate and thorough review of all suicide-related behavior. In addition, physicians and patients should have been notified of the potential for such events to occur. This notification should have included updates to the product labeling and/or a Dear Doctor letter describing suicide-related behaviors in patients receiving gabapentin.

Psychobiological Adverse Events Reported to the SRS Database

	1994 Q4		***1995 Q4***		***1996 Q2***	
Costart Term	**Reports**	**Pct**	**Reports**	**Pct**	**Reports**	**Pct**
Abnormal dreams	1	0.68%	1	0.26%	1	0.20%
Affect lability	1	0.68%	2	0.52%	3	0.60%
Agitation	2	1.35%	5	1.31%	7	1.39%
Anxiety			1	0.26%	2	0.40%
Confusional state	3	2.03%	9	2.35%	12	2.38%
Delirium	1	0.68%	2	0.52%	3	0.60%
Delusion			1	0.26%	1	0.20%
Depersonalisation			1	0.26%	1	0.20%
Depression	1	0.68%	5	1.31%	6	1.19%
Hallucination	2	1.35%	7	1.83%	9	1.79%
Hostility	3	2.03%	6	1.57%	10	1.98%
Major depression	2	1.35%	2	0.52%	2	0.40%
Nervousness	1	0.68%	3	0.78%	4	0.79%
Overdose	4	2.70%	8	2.09%	9	1.79%
Paranoia	2	1.35%	3	0.78%	3	0.60%
Personality disorder	2	1.35%	6	1.57%	7	1.39%
Psychotic disorder	3	2.03%	10	2.61%	11	2.18%
Suicide attempt	**2**	**1.35%**	**5**	**1.31%**	**6**	**1.19%**
Thinking abnormal	3	2.03%	7	1.83%	9	1.79%
Death	5	3.38%	16	4.18%	17	3.37%

WORLD HEALTH ORGANIZATION ADVERSE EVENT DATABASE

118. Psychobiological adverse events reported to the World Health Organization (WHO) Database from 1994 through 1996 were examined. Between 1994 and 1995, substantial increases in the number of events of depression, aggressive reaction, emotional lability, agitation, personality disorder, thinking abnormal and hallucination were observed (see Table below). During that time period no substantial changes were made to the international or US Neurontin product labeling. Pfizer Defendants did examine a number of reports of psychosis observed in patients receiving gabapentin, but concluded that no change was required for the product labeling.

119. The incidence of reports of psychiatric disorders (psychiatric disorder-related reports / total reports) during 1994-1996 was 22% (87/395) in 1994; 18% (201/1116) in 1995; and 16% (82/514) in 1996.

World Health Organization Adverse Event Data – 1994 through 1996

Adverse Event	1994	1995	1996
Suicide Attempt	2	0	0
Depression	1	5	5
Depression (psychotic)	2	0	0
Aggressive Reaction	11	24	11
Depersonalization	3	1	2
Emotional Lability	2	8	3
Agitation	6	13	3
Personality Disorder	2	15	4
Thinking Abnormal	2	7	3
Hallucination	6	12	4
Psychosis	7	7	2

120. Additional documents describing adverse events associated with gabapentin treatment were reviewed. These documents are reviewed here only for the sake of completeness and were not used as primary sources of information for psychobiological adverse events.

121. For example, Research Report 720-03991 summarized adverse events occurring since the fourth safety update for the gabapentin add-on therapy NDA for the following open-label, add-on therapy studies: 877-210PX, 877-210GX, Named Patients, 945-13, 945-14, 945-15, 945-16. The adverse events occurring in the open-label trials listed above were reviewed by the Parke-Davis a Medical Monitor to determine if any unusual or unexpected events occurred. The conclusion from the Research Report states that no unusual or unexpected events were reported from the open-label studies. Psychobiologic adverse events are reflected in the table below:

Suicidal/Overdose/Aggression Events from June 30, 1993 to January 30, 1995 Adverse Event Report (720-03991)

Trial	Patient #	Demog	AE	Dose	Related	Outcome
945-15	26	20, female	Depression, suicide ideation, aggressive behavior	2400 mg/d	Definitely not	Recovered, Recovered, Not Recovered
945-15	38	19, male	Aggressive behavior	3600 mg/d	Possible	Not recovered
945-15	10	28, Male	Overdose of AEDs	3600 mg/d	Unlikely	Recovered
945-15	15	19, Female	Violent behavior, psychological problem, aggressive behavior	2400-3200 mg/d	Definitely not, Possible, unlikely	Recovered, Not recovered, Not recovered

122. Another example of additional documents includes Periodic Reports covering Non-serious events described adverse events associated with gabapentin. These documents encompassing time periods January 1, 1996 through May 31, 1996 and June 1, 1996 through November 22, 1996 are reviewed below.

123. Suicidal, overdose and aggression events are reflected in Pfizer Defendants' Summary of Safety Information of Gabapentin Capsules (720-03732). With respect to overdose, 2 cases of overdose were listed in the TESS Serious Adverse Events Table. Both were considered associated with the drug: one case was from study 945-83 (Center 10, patient 7; age 47; female) - a suicide attempt; the other case appears to be an accidental overdose. With respect to suicidal events, there was one suicidal event (patient 9, center 17; attempted suicide) from study 945-83. With respect to aggression, there was one patient who threatened to stab her brother (patient 001, Center 18).

124. Additional documentation included Investigator Brochures. One such brochure was Investigator's Brochure for Neurontin (Gabapentin, CI-945) for Studies Conducted in the United States (Research Report # RR-X 720-03362 - Issued April 19, 1994). This investigator's brochure consists of 2 major sections: the package insert approved by FDA in December 1993; additional information included to assist investigators conducting clinical trials for new indications. Another brochure was Investigator's Brochure for Neurontin (Gabapentin, CI-945) for Studies Conducted Outside the United States (Research Report # RR-X 720-03381 - Issued May 31, 1994). This investigator's brochure consists of 3 major sections: the package insert approved by the country to which the brochure was sent; Physicians Desk Reference Information; additional information included to assist investigators conducting clinical trials for new indications.

125. The following information was contained in both of the above listed Investigator's Brochures: Under the category: "Unexpected, Possibly Related, Serious Adverse Events Reported to the FDA since US Approval for Add-on Therapy", only 2 events were listed (pancreatitis and subarachnoid hemorrhage). These documents also noted that gabapentin was being evaluated as monotherapy in the treatment of partial seizures with or without secondary generalization as well as monotherapy or add-on therapy in pediatric patients.

126. The following psychobiological adverse events were observed in pediatric patients (n=88) receiving gabapentin; nervousness {5}, thinking abnormal {5}, emotional lability {2}, hostility {2}. No adverse event data from the monotherapy studies in adults was provided.

127. The next Investigator's Brochure (RR-X 720-03480) was issued on April 21, 1997. This document is the first Investigator's Brochure to mention ongoing or planned studies in psychiatric indications, including bipolar disorder. A prudent pharmaceutical company should have updated their Investigators Brochure to more adequately reflect the psychobiological adverse events associated with gabapentin therapy. This would have been especially important during the time period January 1994 through September 1996, because gabapentin trials for non-approved indications were started. The patient population in some of these trials was at increased risk for psychobiological adverse events, and thus physicians/investigators should have been made aware of the large number of serious events associated with gabapentin.

128. Additional information was examined from a **Gabapentin Monotherapy Clinical Expert Report** pertaining to data for 9 clinical trials, 6 of which contribute efficacy and safety data and 3 of which contribute only safety data. Adverse events are not discussed in detail and it is noted that no new safety issues arose. Clinical Monotherapy Studies included the following for the time period 1994 -1996: 945-77; 945-177; 945-88; 945-82; 945-83; 945-89; there was also a Clinical Pharmacology Study: 945-190. The total gabapentin patient population was 674. There were 9 deaths: 3 were considered sudden unexplained deaths (1 of the 3 was considered possibly related to gabapentin (from 945-83). Serious adverse events within the patient population were 73/674 (10.8%) and included the following: Confusion (8); Psychosis (6); and Agitation (3). Withdrawals from studies within the patient population were 52/659 (8%) due to an adverse event. Withdrawals due to Psychobiologic adverse events amounted to 1.1%.

129. A literature review of articles pertaining to gabapentin and published in the medical literature during the observed time period (January 1994 through September 1996) was performed. These articles are listed below.

Neurontin Medical Literature

January 1994 through September 1996

a) 01/1994 Radulovic LL, Wilder BJ, Leppik IE et al **Lack of interaction of gabapentin with carbamazepine or valproate,** Epilepsia, 35: 155-161. *Study design*: Pharmacokinetic study; Number of patients: 12. Relevant adverse events reported in the publication: no psychobiologic adverse events reported

b) 05/1994 **US Gabapentin Study Group The long-term safety and efficacy of gabapentin (Neurontin) as add-on therapy in drug-resistant partial epilepsy**., Epilepsy Res, 18: 67-73. *Study design*: Open-label, add-on therapy; number of patients: 240. Relevant adverse events reported in the publication: depression {2, both patients withdrew}, nervousness.

c) 07/1994 Anhut H, Ashman P, Feuerstein TJ et al **Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. The International Gabapentin Study Group**, Epilepsia, 35: 795-801. *Study design*: Double-blind, placebo-controlled (all patients were on 1-2 other Antiepileptic drugs). Number of patients: 272. Relevant adverse events reported in the publication: No psychobiologic adverse events reported.

d) 09/1994 Handforth A and Treiman **DM Efficacy and tolerance of long-term, high-dose gabapentin: additional observations**, Epilepsia, 35: 1032-1037. *Study design*: Open-label; Gabapentin as add-on therapy. Number of patients: 23. Relevant adverse events reported in the publication: lethargy {5; 2 positive rechallenges}, jitteriness {2}

e) 10/1994 Sivenius J, Ylinen A, Kalviainen R et al **Long-term study with gabapentin in patients with drug-resistant epileptic seizures**, Arch Neurol, 51:

1047-1050.*Study design*: Open-label; Gabapentin as add-on therapy. Number of patients: 25. Relevant adverse events reported in the publication: irritability and aggression (in the same patient – with a positive dechallenge for both)

f) 05/1995 Short C and Cooke L **Hypomania induced by gabapentin**, *Br J Psychiatry*, 166: 679-680. A case report of a 49 year old man developing hypomania while on gabapentin. This report describes an apparent positive dechallenge event and suggests that caution be taken when administering gabapentin to patients with a past history of psychiatric disorder.

g) 07/1995 Ben Menachem E, Soderfelt B, Hamberger A et al **Seizure frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures**, Epilepsy Res, 21: 231-236. *Study design*: Double-blind, placebo-controlled (all patients were on at least 1 other Antiepileptic drug). Number of patients: 36. Relevant adverse events reported in the publication: None mentioned

h) 09/1995 Morris GL, III **Efficacy and tolerability of gabapentin in clinical practice**, Clin Ther, 17: 891-900. *Study design*: Retrospective; Gabapentin as add-on therapy. Number of patients: 100. Relevant adverse events reported in the publication: aggression, agitation, severe lethargy.

i) 01/1996 Petroff OA, Rothman DL, Behar KL et al **The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy**, Ann Neurol, 39:95-99. *Study design*: Pharmacokinetic study. Number of patients: 25. Relevant adverse events reported in the publication: Adverse events were not discussed.

j) 02/1996 Dixit SN, Jain S, Padma MV et al **Gabapentin in refractory partial epilepsy—a trial in India**, Acta Neurol Scand, 93: 85-87. *Study design*: Open-label, add-on therapy. Number of patients: 26. Relevant adverse events reported in the publication: memory problems {4}

k) 02/1996 Gidal BE, Maly MM, Budde J et al **Effect of a high-protein meal on gabapentin pharmacokinetics**, Epilepsy Res, 23: 71-76. *Study design*: Pharmacokinetic study; randomized, crossover. Number of patients:10. Relevant adverse events reported in the publication: No psychobiologic adverse events noted

l) 03/1996 Rosner H, Rubin L, and Kestenbaum A **Gabapentin adjunctive therapy in neuropathic pain states**, Clin J Pain, 12: 56-58. *Study design*: Case series. Number of patients: 4. Relevant adverse events reported in the publication: No psychobiologic adverse events noted

m) 04/1996 Dimond KR, Pande AC, LaMoreaux L et al **Effect of gabapentin (Neurontin) [corrected] on mood and well-being in patients with epilepsy**, Prog Neuropsychopharmacol Biol Psychiatry, 20: 407-417. *Study design*: Review of 5 double-blind, add-on trials (877-210P; 945-5, -6, -9, -10). Number of patients: 705. Relevant adverse events reported in the publication: None reported; only discussed beneficial effects of gabapentin on mood and well being ***"… an exploration of the psychiatric uses of gabapentin is warranted."***

n) 04/1996 Stahl JS, Rottach KG, Averbuch-Heller L et al **A pilot study of gabapentin as treatment for acquired nystagmus**, Neuroophthalmology, 16: 107-113. *Study design*: Pilot study. Number of patients: 3. Relevant adverse events reported in the publication: Adverse events were not discussed.

o) 05/1996 Perry JR and Sawka C **Add-on gabapentin for refractory seizures in patients with brain tumours**, Can J Neurol Sci, 23: 128-131. *Study design*: Open-label, add-on. Number of patients: 14. Relevant adverse events reported in the publication: No psychobiologic adverse events noted.

p) 06/1996 Khurana DS, Riviello J, Helmers S et al **Efficacy of gabapentin therapy in children with refractory partial seizures,** J Pediatr, 128: 829-833. *Study design*: Open-label, add-on. Number of patients:32. *Relevant adverse events reported in the publication*: behavioral adverse events were noted in 15 patients (4 cases required physician intervention – 1 pt became more withdrawn, 3 pts became more aggressive with increased mood swings; in 3 / 4 of these patients there was a positive dechallenge).

q) 05/1994 Fischer JH, Barr AN, Rogers SL et al Lack of serious toxicity following gabapentin overdose, Neurology, 44: 982-983. 16 year old girl ingested 48.9 grams of gabapentin which was prescribed to her father. The subject recovered.

r) 1995 Trudeau VL, Dimond KR, Smith FB, et al. **Gabapentin (GBP; Neurontin®) monotherapy compared with carbamazepine (CBZ) monotherapy and combination GBP plus CBZ (GBP/CBZ) therapy in patients with medically refractory partial seizures: a 3-way crossover trial (945-36).** Epilepsia, 36(Suppl 4):68. The adverse event profile for gabapentin monotherapy was similar to that of gabapentin combined with carbamazepine. Preliminary analysis showed superior performance on most neuropsychological parameters among patients receiving gabapentin alone.

s) 1997 Bergey GK, Morris HH, Rosenfeld W et al **Gabapentin monotherapy: I. An 8-day, double-blind, dose-controlled, multicenter study in hospitalized patients with refractory complex partial or secondarily generalized seizures. The US Gabapentin Study Group 88/89**, *Neurology*, 49: 739-745.

t) 1999 Beydoun A **Monotherapy trials with gabapentin for partial epilepsy**, *Epilepsia*, 40 Suppl 6: S13-S16.

u) 1997 Beydoun A, Fischer J, Labar DR et al **Gabapentin monotherapy: II. A 26-week, double-blind, dose-controlled, multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily**

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aa) 1997 Leach JP, Girvan J, Paul A et al **Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy**, *J Neurol Neurosurg Psychiatry*, 62: 372-376.

bb) 1999 Mayer T, Schutte W, Wolf P et al **Gabapentin add-on treatment: how many patients become seizure-free? An open-label multicenter study**, *Acta Neurol Scand*, 99: 1-7.

cc) 1992 Wilensky, A. J., Temkin, N. R., Ojemann, L. M., Ricker, B., Holubkov, A., Rainwater, M., and Shellenberger, K. **Gabapentin and carbamazepine as monotherapy and combined: A pilot study.** Epilepsia 33[*Suppl* 3], 77.

NEURONTIN PRECLINICAL STUDIES

130. Finally, additional documents describing preclinical studies are summarized below. For example, attention is referenced to Research Report #740-02959 (Issued 5/23/1991), **The Effects of Gabapentin in the Water Wheel Behavioral Despair (WWBD) Test.** This study assessed the effects of gabapentin on wheel turning behavior in the water wheel behavioral despair test, a test for presumed antidepressant activity. Results of the study demonstrated that **Gabapentin did not significantly affect wheel turning behavior in the WWBD test; thus it did not have antidepressant properties.** The known antidepressant imipramine significantly facilitated wheel turning behavior.

131. Research Report #740-03075 (Issued 10/19/1992), **The Effects of Gabapentin in the Water Wheel Behavioral Despair (WWBD) Test After 9 Days of Chronic Dosing** was reviewed. Results of the study demonstrated that Neurontin did not affect wheel turning behavior and thus did not resemble the effect of known antidepressants in this procedure.

132. In Research Report #770-00286 (Issued 3/7/1995), **The Anxiolytic and Antinociceptive Profiles of Gabapentin and the Reversal by *D*-Serine,** the study was performed to investigate the pharmacological profile of Gabapentin in animal models of anxiety and analgesia. Gabapentin was shown to produce anxiolytic-like effects in four animal models of anxiety (rat conflict test, mouse light/dark box, rat elevated X-maze and the marmoset human threat test).

133. In Research Report #740-03253 (Issued 8/30/1995), **Evaluation of Gabapentin for Potential Anxiolytic Activity Using a Water Lick Conflict Test**, Gabapentin was shown to have anxiolytic properties similar to that of a reference anxiolytic drug (chlordiazepoxide).

134. The regulatory-related events relating to Dr. David Franklin also began in 1996. Dr. Franklin began his four month employment with Pfizer Defendants as a Medical Liaison in 1996. During that short time period, he witnessed a variety of events that prompted him to leave Pfizer Defendants and file a lawsuit under the False Claims Act for multiple illegal Neurontin marketing practices. Several years later, Pfizer Defendants reached a global settlement with U.S. and state authorities for multiple illegal actions relating to Neurontin. These settlement provisions included guilty pleas for violations of the Food Drug and Cosmetic Act. In particular, Pfizer Defendants (Warner Lambert) pled guilty to violations of Title 21 United States Code Sections 331(a), 331(d), 333(a), 352(f)(1) and 355.

135. Pfizer Defendants had designed a corporate initiative to promote more than 30 lucrative off-label indications for Neurontin. However, there were no plans to seek regulatory approvals for these claimed cases. Rather, a publication strategy was developed to disseminate articles describing the benefits of Neurontin for these off label uses (*i.e.*, "create a drumbeat in the literature").[50] This action was coupled with the employment of a wide network of paid healthcare professionals to publicly promote these off-label uses.

136. Pfizer Defendants were well aware that the off label uses were not adequately studied for safety and efficacy. In fact, many of the indications lacked a scientific rationale to even theoretically support the proposed use. In some of the Pfizer-sponsored studies of off-label uses, Neurontin was shown to provide less clinical benefits than either placebo therapy or other available drug products.[51]

137. Notwithstanding this dearth of supporting safety data, Pfizer Defendants required their representatives to promote extraordinarily high (and untested) doses of Neurontin for these off-label uses. Although the product was only approved for daily doses ranging from 900 mg/day to 1800 mg/day, the representatives were told that management did not "want to see a single patient coming off Neurontin before they have been up to at least 4800 mg/day."[52] Simultaneously, the management also noted they didn't want "to hear that safety crap either."[53]

138. Importantly, Pfizer Defendants were already aware in 1996 of the increases in psychobiological adverse events associated with higher doses (Study 945-190; Section 3).[54] These events would have been particularly concerning for the thousands of patients receiving gabapentin for the promoted off-label psychiatric uses including

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[50] *See* WLC_FRANKLIN_0000087284-93

[51] *See* Pande AC, Crockatt JG, Janney CA *et al* *Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group*. Bipolar Disord, 2: 249-255.

[52] *See* Pfizer_JSu_0023289-0023314 at 0023303

[53] *See* Affidavit of David Franklin, Ph.D., dated May 19, 2003 at p5 (Exhibit to Relator's Opposition to Deft's Motion for Summary Judgment and Supporting Material, Untied States of America ex rel. David Franklin, v. Pfizer, Inc., and Parke-Davis a Division of Warner-Lambert Co.). *See* also Pfizer_JSu_0023289-0023314 at 0023303

[54] Study 945-190 (RR 744-00238) was a study entitled, "A multiple-dose, dose-proportionality study of Neurontin® (gabapentin; CI-945) capsules in healthy volunteers (Protocol 945-190-0). The clinical trial dates encompassed January 23, 1995 through February 27, 1995. Among the psychobiologic adverse events deemed associated with Neurontin included Depersonalization (9); Abnormal thinking (6); Euphoria (4); Hyperkinesia (3); Agitation (2); Nervousness (2); Confusion (1); Personality disorder (1).

bipolar depression, anxiety disorders, panic disorders, OCD, dementia, addictions, and many others.

DECHALLENGE EVENTS ASSOCIATED WITH NEURONTIN 1994-1996

139. As noted in this discussion, Pfizer's off-label marketing actions are particularly concerning when the numbers of positive dechallenge events and the wide variety of gabapentin indications being assessed is considered. As noted earlier, a positive dechallenge event refers to the partial or complete disappearance of an adverse event following the withdrawal of a product. This can represent evidence that the drug under study was responsible for or associated with the adverse event. A number of positive dechallenge events in patients experiencing psychobiological adverse events with gabapentin use were found. This evidence further supports the association of gabapentin with psychobiological adverse events in patients receiving this therapy. Pfizer Defendants should have examined these events more closely to determine their relationship to gabapentin, particularly as the drug gained wide acceptance for use in non-indicated conditions such as bipolar disorder and neuropathic pain.[55]

140. A more thorough examination of these positive dechallenge events, coupled with a review of the various adverse event databases discussed later in this report, should have alerted Pfizer Defendants to make changes to the gabapentin product labeling to reflect the large number of psychobiologic adverse events associated with this drug. Because the psychobiological events are believed to contribute to eventual suicide-related behavior, it is important to study this constellation of adverse events and not just isolated suicide events.

141. The following summary of positive dechallenge data were obtained from the Pfizer Defendants' clinical research reports provided in the accompanying tabular summaries. Interestingly, only two (2) of these events were considered "not related" to gabapentin by the clinical investigator. The tables below list the individual events and the trials in which they occurred.

[55] Importantly, 21 CFR 201.57 (2007) provides that a product's "labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard"(emphasis added). Given the circumstances of psychobiologic adverse events associated with Neurontin usage, and that there was widespread use of Neurontin for indications "not provided for under the 'Indications and Usage" section, the Pfizer Defendants should have revised the product's labeling appropriately.

Positive Dechallenge Events Associated with Neurontin (1994-1996)

ADVERSE EVENT	# POSITIVE DECHALLENGES
Hostility	9
Emotional Lability	6
Thinking Abnormal	6
Nervousness	5
Confusion	5
Hyperkinesia	2
Suicidal	1 (Pediatric patient)
Personality Disorder	1
Agitation	1
Hypomania	1
Depression	1
Frustration	1

Positive Dechallenge Events Associated with Gabapentin Therapy (Pediatric Trials)

Trial	Patient/ Center Number	Dose (mg/kg/day) (mg/day)	Adverse Event	Relationship	Outcome
Epilepsy (Pediatric Trials)					
945-094	11/9	27.5	Emotional lability	Possibly	Recovered
945-094	1/27	27.6	Hyperkinesia	Possibly	Recovered
945-094	5/28	28.1	Hyperkinesia	Probably	Recovered
			Emotional lability	Probably	Recovered
			Thinking abnormal	Probably	Recovered
945-094	3/48	25.9	Emotional lability	Possibly	Recovered
945-094	2/11	1800	Suicidal	Definitely Not	Recovered
			Hostility	Definitely Not	Recovered
945-095	3/8	36.4	Emotional lability	Possibly	Recovered
945-095	2/24	34.0	Emotional lability	Possibly	Recovered
945-095	1/52	56.5	Hostility	Possibly	Recovered
945-87	1/3	31.0	Emotional lability	Definitely	Recovered
945-87	1/6	Not given	Thinking abnormal	Probably	Recovered
			Hostility	Probably	Recovered
945-87	2/6	28.0	Nervousness	Definitely	Recovered
945-87	6/6	30.0	Personality disorder	Definitely	Recovered
			hostility	Definitely	Recovered
945-87	2/21	30.0	Confusion	Probably	Recovered
945-187	7/29	26.0	Hostility	Probably	Recovered
945-86	7/16	20.0	Thinking abnormal	Probably	Recovered
			Agitation	Probably	Recovered
			hostility	Probably	Recovered
945-86	11/17	32.0	Hostility	Definitely	Recovered

Positive Dechallenge Events Associated with Gabapentin Therapy
(*continued*)
Adult Epilepsy Trials (Monotherapy and Add-On) and Diabetic Neuropathy

Trial	Patient/ Center Number	Dose (mg/kg/day) (mg/day)	Adverse Event	Relationship	Outcome
Epilepsy (Monotherapy)					
945-83	5/8	1200	Thinking abnormal	Possibly	Recovered
945-83	7/10	3300	Hypomania	Possibly	Recovered
945-83	14/10	3600	Hostility	Possibly	Recovered
945-83	4/11	3600	Depression	Probably	Recovered
			Nervousness	Probably	Recovered
			Hostility	Probably	Recovered
945-82	1/10	2400	Confusion	Possibly	Recovered
945-82	5/19	2400	Nervousness	Probably	Recovered
			Frustration	Probably	Recovered
Epilepsy (Add-On Therapy)					
945-90	2/84	Not given	Confusion	Probably	Recovered
945-90	2/87	Not given	Thinking abnormal	Definitely	Recovered
945-90	3/172	Not given	Nervousness	Possibly	Recovered
945-90	2/182	Not given	Confusion	Definitely	Recovered
945-90	3/33	Not given	Nervousness	Unlikely	Recovered
945-90	1/43	Not given	Confusion	Possibly	Recovered
Diabetic Neuropathy					
945-210	4008/4	900	Thinking abnormal	Possibly	Recovered

REGULATORY EVENTS 1994-1996

142. A review of the Pfizer Defendants' databases and FDA records indicate there was only one minor label change between January 1993 and September 1996. On November 14, 1994, Pfizer Defendants received approval for NDA Supplement 001, submitted on July 6, 1994. This new labeling reflected a corrected incidence number for status epilepticus reports in the pre-marketing clinical studies (Warnings Section). Pfizer Defendants also submitted two CMC-related supplements that were not associated with any labeling revisions. No new Neurontin indications or formulations were approved.

143. There were several FDA communications and interactions relating to Neurontin promotional pieces during the time period of 1994-1996. These early letters primarily relate to FDA's concern with promotion of off-label uses and Pfizer's improper positioning of Neurontin relative to other antiepileptic agents.[56] FDA's letter, dated July 18, 1996, clearly establishes FDA's concerns with the continued promotion of off-label uses and the use of company-solicited physician participation in teleconference series.[57]

[56] *See* WLC_FRANKLIN_0000053292-53300; X022545-555; WLC_FRANKLIN_0000038943-45; WLC_FRANKLIN_0000041293-96; WLC_FRANKLIN_0000041500-6; WLC_FRANKLIN_0000053306-9; WLC_FRANKLIN_0000041507-10.

[57] *See* WLC_FRANKLIN_0000053292-53300.

CONCLUSIONS 1994-1996

144. Gabapentin has been tested in several animal models of anxiety. In two of these studies, no antidepressant properties were demonstrated. In one published study, gabapentin was found to produce anxiolytic-like effects in 4 separate anxiety-producing paradigms (rat conflict test, mouse light/dark box, rat elevated X-maze and the marmoset human threat test). An additional study using the Water Lick Conflict Test demonstrated that gabapentin has anxiolytic properties similar to chlordiazepoxide, a reference anxiolytic.

145. From these studies, the use of gabapentin in psychiatric indications is not warranted. Combined with clinical study and postmarketing reports of suicide, depression, aggression, hostility and other psychiatric events, administration of gabapentin to a population already at risk for these events was and remains an irresponsible course of action.

146. As previously described in this report, Pfizer Defendants marketed Neurontin for a wide variety of lucrative off-label psychiatric uses during the aforementioned time period 1994 – 1996. Successful clinical trials were not available to the Pfizer Defendants prior to their off-label marketing initiatives. Rather, the Pfizer Defendants' plan was to create and promote these uses based on subsidized physician endorsements. Pfizer Defendants likely did not attempt to obtain the legally-required FDA pre-clearance for these uses because they knew that the fundamental benefit-risk assessments could not be established.

147. The clinical benefits of Neurontin for these indications were not established with two well controlled clinical trials. In some instances, Pfizer Defendants generated no clinical data at all. In other instances, Pfizer Defendants attempted trials but found Neurontin did not provide as much clinical effectiveness as placebo therapy or other FDA-approved products.

148. With respect to risks, the adverse event data generated in the initial marketing years did not support the high-selling psychiatric indications. As noted earlier, Pfizer Defendants were aware that Neurontin was associated with problematic psychobiologic events in both controlled trials and in post-marketing surveillance databases. These events included suicide, suicidal-related events, depression, nervousness, depersonalization, and many others. Obviously, these events should have precluded the use of Neurontin for the lucrative bipolar depression, anxiety, phobia, and other related psychiatric indications. Unfortunately, this did not occur.

149. Clearly, Pfizer Defendants could not establish either the necessary benefit or risk parameters needed for these indications to be properly reviewed by FDA. As such, acceptable benefit-risk assessment would be impossible to achieve for these indications. Absent these assessments, Pfizer Defendants still elected to market Neurontin for psychiatric uses as well as a number of neuropathic pain conditions. Unfortunately, these decisions probably resulted in the startling numbers of post marketing psychiatric adverse events reported over the next several years.

150. Pfizer Defendants failed to reasonably warn healthcare professionals of Neurontin's lack of efficacy, particularly pertaining to "off-label" psychiatric uses. With the presence or absence of Pfizer Defendants' illegal promotional scheme for

"off-label" uses, Pfizer Defendants knew of the widescale use of Neurontin for "off-label" psychiatric uses and should have reaosonably warned about its lack of efficacy.

151. Pfizer Defendants did not amplify the adverse event data in their Neurontin professional labeling over the initial three years following market approval. As such, neither prescribers nor their patients were able to make fully informed decisions regarding the acceptability of Neurontin for its approved use as adjunctive anti-epileptic therapy.

152. By late 1996, Pfizer Defendants should have included the growing numbers of new and previously recognized psychobiologic events. The labeling should have specifically highlighted these data in the Warnings, Precautions and Postmarketing Adverse Event sections of the insert. Following launch, it is not acceptable to ignore new events or relegate escalating frequencies of previously reported events to the Adverse Events section relating to Controlled Clinical Trial Data. Physicians and patients often disregard or minimize this labeling section because it is perceived that the events included herein are restricted to the prelaunch experiences.

153. It is clear from a review of sources during the above referenced time-frame (1994-1996) that there were a significant number of psychobiologic adverse events reported which were associated with the use of gabapentin. The relationship of these psychobiological adverse events to gabapentin therapy is supported by numerous examples of positive dechallenge/rechallenge data and their occurrence in a number of postmarketing surveillance databases. Further, in a number of placebo-controlled clinical trials, patients receiving gabapentin demonstrated higher rates of adverse events related to both the nervous system and psychobiological function.

154. Regarding the occurrence of notably serious adverse events (such as those related to suicide), it is clear that Pfizer Defendants either chose to omit or misclassify certain events in order to avoid regulatory scrutiny. This included the misclassification of several suicide-related events from the large STEPS trial and the failure to code an intentional overdose from an additional trial (945-083) as a suicide attempt. While Pfizer Defendants did commission a perfunctory review of psychosis associated with gabapentin in May 1995 (*e.g.*, Michael Trimble report), this report concluded that gabapentin was not associated with the occurrence of psychosis in only a few specific cases. This report however, failed to consider additional psychobiological events including those related to suicidal behavior (*i.e.*, suicidal thoughts, suicidal tendencies, intentional overdose, and completed suicide).

155. A more thorough review of psychobiological adverse events should have been performed, and following this, appropriate changes should have been made to the product labeling to more adequately reflect the risks associated with gabapentin therapy. This became particularly important during the time period reviewed in this section (1994-1996) as Pfizer Defendants illegally marketed off-label psychiatric indications for gabapentin in patient populations susceptible to psychobiologic adverse events (*i.e.*, those with various mood disorders). The fact that patients and prescribers were not warned of these serious risks represents negligent behavior on the part of Pfizer Defendants.

156. It is well-recognized that use of a drug product in multiple patient populations (especially non-labeled patient groups) complicates the determination of its safety. This mandates that pharmaceutical manufacturers maintain a rigorous evaluation of all safety signals, particularly serious adverse events related to suicide. For example, one drug-induced serious adverse event occurring in patients receiving a drug for an off-label indication is new-onset seizures associated with the use of Gabitril®. Based

on 59 post-marketing reports, Cephalon, the manufacturer of Gabitril®, warned patients and prescribers of this risk in a February 2005 Dear Dr. Letter.[58] In the present case, despite numerous reports of suicide, suicide attempts and intentional overdoses, similar actions were not undertaken by Pfizer Defendants for instances of suicide attempt or completed suicide reported in patients taking Neurontin.

[58] *See* www.fda.gov/cder/drug/advisory/gabitril.htm, dated February 18, 2005, at which time FDA stated, "the Agency has become aware of reports of the occurrence of seizures in more than 30 patients prescribed Gabitril for conditions other than epilepsy. Most of these uses were in patients with psychiatric illnesses. Such so-called *off label* prescribing is a common practice among physicians. Because of the risk of seizures, however, in addition to adding the Bolded Warning to product labeling, the sponsor has agreed to undertake an educational campaign targeted to healthcare professionals and patients in which such *off label* use will be discouraged".

IV(c) Review of Psychobiological Adverse Events: October 1996 - May 2002

157. This report will now address the time period from October 1996 through May 2002, with an emphasis on Pfizer Defendants' pursuit of the FDA approval for post herpetic neuralgia. The Integrated Summary of Safety (ISS) document submitted by Pfizer Defendants in support of the gabapentin NDAs (21-397; 21-423; 21-424) for the treatment of post herpetic neuralgia is reviewed below.[59]

158. The ISS document reviews patient safety information related to gabapentin use in five controlled neuropathic pain studies, two of which were pivotal studies in patients with post herpetic neuralgia. In addition, this document reviews four other ongoing neuropathic pain studies, two clinical pharmacology studies and eight combination studies assessing gabapentin when administered with either naproxen or hydrocodone. Of note, although Pfizer Defendants had hoped to secure an approval for the treatment of generalized neuropathic pain, this was denied by FDA (May 2001) due to insufficient data. Subsequent to this, Pfizer Defendants submitted the noted three NDAs for the post herpetic neuralgia pain indication and these were approved by FDA on May 24, 2002.

159. Finalized study data for the trials noted in the Pfizer Defendants' post herpetic neuralgia Integrated Summary of Safety (ISS) were reviewed.[60] This was required as pertinent clinical trial records at the interim points in time selected by Pfizer Defendants could not be accessed. In addition, additional studies not covered in the Pfizer Defendants' ISS, including those performed by Pfizer Defendants in epileptic patients, patients with migraine headache and several clinical pharmacology studies were reviewed. These studies should have been included in the 2001 ISS document. The most significant ISS changes, set forth below, correct Pfizer Defendants' less-than-complete presentation of all available safety data concerning self-injury and suicide-related events. As such, the Pfizer Defendants' ISS Study Reviews were expanded to include all pertinent data relative to adverse psychobiologic events observed in patients receiving gabapentin.

160. The Pfizer Defendants' ISS also focused its postmarketing safety review on events found to occur in 2% or more of the neuropathic pain patients and events for which Neurontin was the primary suspect medication. Adverse events occurring in less than two percent of the patients or from other available databases were not provided in this document. Given the suicide-related concerns evidenced prior to 2001, Pfizer Defendants should have provided an overview of all available data (especially life-threatening events) before expanding the indicated patient populations. By arbitrarily limiting their overview of postmarketing events, Pfizer Defendants failed to provide patients a clear picture of the growing suicide risks.

161. In order to address postmarketing safety data, an overview of all available databases is provided in this report. These data have been compiled from multiple sources including the scientific literature, Periodic Safety Update Reports (PSURs), Annual Reports, Adverse Event Databases (including the Pfizer Defendants' internal database, World Health Organization, Spontaneous Reporting System/Adverse Events Reporting System (SRS/AERS) and other databases.

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[59] It appears that Pfizer submitted 3 different NDAs for the post herpetic neuralgia indication and each NDA provided for a different oral dosage form (capsules, tablets, solution).

[60] *See* 720-30135

162. This section provides a review of psychobiologic adverse events including overdose and suicide-related behaviors in patients receiving gabapentin therapy and presented in PSURs prepared by Pfizer Defendants (Parke-Davis). Eight PSUR documents were reviewed for patient adverse events occurring during the time period covered in this time-period review (October 1996 - May 2002). In the tables below summaries of the suicide-related events and all other relevant psychobiologic events are provided. The PSUR documents include cases of adverse events reported spontaneously to Pfizer Defendants, cases reported from healthcare providers, cases published in the medical literature and cases reported from clinical studies, regardless of causality. The current timeline (October 1996 - May 2002) does not align precisely with the date of the PSURs reviewed for this report (January 1, 1997 – January 2003). As such, psychobiologic adverse events occurring from October 1996 to December 1996 were reviewed and comments were made in the previous time period section. In addition, psychobiologic adverse events were summarized from a 5 year PSUR document (February 1, 1998 to January 2003) although some of these events occurred after our imposed cutoff date of May 2002.

163. The following table provides a listing of suicide-related adverse event terms found in PSUR documents during the subject reporting period. These events began to appear consistently in PSUR documents starting in 2000 and early 2001 and culminated in large numbers of reports of suicide ideation (19), suicide attempt (14), and suicide (12) in the 5 year PSUR document (1998-2003).

164. A review of the psychobiologic adverse event data from these PSUR documents reveals a number of interesting trends (Table below). For example, the number of intentional overdoses more than doubles (from 5 reports to 12) in the 2000-2001 time period. Other frequently-reported events in the semi-annual reports include confusion, hallucination, thinking abnormal, depression and anxiety. In addition, data from the 1998-2003 PSUR indicate that nearly 27% of the 14,761 reported adverse events occurred either in the central and peripheral nervous system (14.6%) or were psychiatric-related events (12.0%). Adverse events of note from this 5 year PSUR include a large number of intentional overdose events (422 – *see explanation below*), suicide (12 events), suicide ideation (19 events), suicide attempt (14 events), suicidal thoughts (3 events) and suicidal / suicidal tendency (6 total events). There were also 84 reports of agitation, 57 reports of nervousness and 40 reports (or more) of psychosis, aggression, emotional lability, depersonalization and personality disorder.

Intentional Overdose Events

165. Pfizer Defendants discussed overdose cases in their PSUR documents (*i.e.*, see the 8/1/00 – 1/31/01 and 2/1/01 – 7/31/01 PSUR documents). In addition, the 5 year PSUR provides a summary detailing the large number of overdose events (422 total) observed during this period. This number does not coincide with the data provided in individual PSUR reports during this 5 year period. Pfizer Defendants do note that their convention is to code both intentional overdose and drug maladministration when a patient is prescribed a dose higher than what is recommended in the US label (1800 mg/day). However, it is not clear what types of overdose (*i.e.*, intentional, accidental) are included under this term. Of these 422 cases Pfizer Defendants report, 297 were attributed either to another drug (other than gabapentin) or there was

no report of a daily dose in excess of the label recommendation. For these 297 reports, Pfizer Defendants performed no further analysis.

166. Of the remaining 125 cases (124 of which were reported spontaneously), 116 were coded as intentional overdose. The following list provides a breakdown of the 125 cases Pfizer Defendants did not exclude:

- prescriptions for higher doses than the label recommendation (65 cases)
- overdoses involving gabapentin and at least one other medication (29 cases)
- overdoses of gabapentin alone (17 cases - 10 of which were "intentional")
- renally-impaired or dialysis patients (5 cases)
- cases not falling into the other four categories (9)

167. Pfizer Defendants chose not to discuss in detail those intentional overdose events that appeared to be attempts at self-harm (*i.e.*, suicide attempts). These include 10 "intentional" overdoses of gabapentin alone as well as the 29 cases where another medication (besides gabapentin) was involved. Pfizer Defendants' discussion of overdose events emphasized the non-serious cases (*i.e.*, those where the event was attributed to another drug or there was no report of a daily dose in excess of the label recommendation). Pfizer Defendants deemphasized the intentional overdose events which may have represented some suicide attempts under the much larger number of non-serious overdoses.

Suicide-related Adverse Events from PSUR's

Adverse Event	1/1/97-7/31/97	8/1/97-12/31/97	2/1/99-7/31/99[#]	8/1/99-1/31/00	2/1/00-7/31/00	8/1/00-1/31/01	2/1/01-7/31/01	2/1/98-1/03[*]	Total
Intentional Overdose[&]	1	0	1	4	5	12	11	372	406
Suicide Attempt	0	0	2	2	0	2	3	14	23
Suicide Ideation	0	0	0	1	1	1	0	19	22
Suicide	1	0	0	0	1	1	1	12	16
Suicidal Thoughts	1	0	0	0	0	2	1	3	7
Suicidal	0	0	0	0	0	0	0	4	4
Suicidal Tendency	0	0	0	0	0	0	1	2	3

[#]Psychobiologic adverse events for these PSURs represent cases occurring in the United States only.
*This PSUR covers 5 years (1998-2003) and includes adverse event reports listed previously in other PSUR's.
[&]These events are not necessarily suicide attempts.

Psychobiologic Adverse Events from PSUR's

Adverse Event	1/1/97-7/31/97	8/1/97-12/31/97	2/1/99-7/31/99[#]	8/1/99-1/31/00	2/1/00-7/31/00	8/1/00-1/31/01	2/1/01-7/31/01	2/1/98-1/03[*]	Total
Intentional Overdose[&]	1	0	1	4	5	12	11	372	406
Confusion	3	2	4	6	8	10	8	97	138
Hallucinations	2	1	4	4	7	11	11	**94**	134
Thinking Abnormal	0	0	0	0	0	0	13	119	132
Depression	1	0	5	4	7	10	13	**84**	124
Anxiety	0	0	6	2	4	5	3	**93**	113
Withdrawal Syndrome	0	2	7	6	10	15	2	**76**	118
Agitation	1	0	0	3	1	4	3	**84**	96
Overdose	0	0	1	3	2	3	26	42	77
Nervousness	0	1	2	3	0	4	8	**57**	75
Psychosis	0	0	1	2	2	4	4	**40**	63
Aggression	4	1	1	0	0	2	2	**50**	60
Emotional Lability	0	0	3	0	0	2	0	**55**	60
Depersonalization	0	0	0	0	0	0	0	**56**	56
Manic Episodes	0	0	0	0	0	0	5	**42**	47
Personality Disorder	0	0	0	0	1	0	0	**39**	40
Mood Swings	1	0	1	1	5	7	2	17	34
Irritability	1	1	2	0	2	0	2	19	27
Dementia	2	0	0	0	0	0	0	**25**	27
Suicide Attempt	0	0	2	2	0	2	3	**14**	23
Neurosis	0	0	0	0	0	0	0	**23**	23
Paranoia	0	0	1	1	0	1	6	**13**	22
Suicide Ideation	0	0	0	1	1	1	0	**19**	22
Delusion	0	1	2	0	0	2	4	**8**	17
Suicide	1	0	0	0	1	1	1	**12**	16
Hostility	0	0	3	0	0	0	4	6	13

[#]Psychobiologic adverse events for these PSURs represent United States cases only.

*This PSUR includes adverse event reports listed previously in other PSUR's. Numbers in bold taken from Pfizer Defendants PSUR 'APPENDIX IIIa Summary Tabulation of Adverse Events by WHO Body System and WHO-ART Preferred Adverse Event Term'

[&]These events are not necessarily suicide attempts.

Psychobiologic Adverse Events from PSUR's (*continued*)

Adverse Event	1/1/97-7/31/97	8/1/97-12/31/97	2/1/99-7/31/99[#]	8/1/99-1/31/00	2/1/00-7/31/00	8/1/00-1/31/01	2/1/01-7/31/01	2/1/98-1/03[*]	Total
Delirium	1	1	0	1	2	1	0	4	10
Anxious	0	1	1	0	0	1	0	6	9
Psychotic Features	0	0	0	1	0	0	3	4	8
Suicidal Thoughts	1	0	0	0	0	2	1	3	7
Anger	1	0	0	1	0	2	0	2	6
Post Traumatic Stress Disorder	0	0	1	0	0	2	0	2	5
Behavioral Changes	0	1	0	1	1	0	2	0	5
Bipolar Symptoms	0	0	1	0	0	0	0	4	5
Suicidal	0	0	0	0	0	0	0	4	4
Psychomotor Agitation	0	0	0	0	2	0	0	2	4
Behavior Problems	2	0	0	0	0	0	0	2	4
Abnormal Behavior	1	1	0	0	0	0	1	0	3
Combative	0	0	0	1	0	0	0	2	3
Violent Behavior	0	1	0	0	0	0	0	2	3
Suicidal Tendency	0	0	0	0	0	0	1	2	3
Mental Change	0	0	0	0	0	2	0	0	2
Psychiatric Diagnosis	0	0	1	0	1	0	0	0	2
Homicidal	0	0	0	0	0	0	0	2	2
Acute Psychotic Dysfunction	1	0	0	0	0	0	0	0	1
Assaultive Behavior	0	0	0	0	0	0	0	1	1
Confrontational	0	0	0	1	0	0	0	0	1
Homicidal Ideation	0	0	0	0	0	0	1	0	1
Manic Depression	0	0	0	0	0	0	0	1	1
Neurologic Deficit	0	1	0	0	0	0	0	0	1
Psychotic Reaction	0	0	0	1	0	0	0	1	1
Violent	0	0	0	0	0	0	0	1	1

[#]Psychobiologic adverse events for these PSURs represent cases occurring in the United States only.

*This PSUR includes adverse event reports listed previously in other PSUR's. Numbers in bold taken from Pfizer Defendants PSUR 'APPENDIX IIIa Summary Tabulation of Adverse Events by WHO Body System and WHO-ART Preferred Adverse Event Term'

ANNUAL REPORTS – PERIODIC ADVERSE EVENT REPORTS

168. Neurontin is listed under multiple IND and NDA numbers and each of these are assigned to either a unique indication or a unique dosage form. Using these IND and NDA numbers, the provided database was searched for all Quarterly and Annual Reports (including Periodic Adverse Event Reports) pertaining to gabapentin during the years from 1996 to 2002. These reports were then evaluated for suicide-related and psychobiologic events. A total of 29 NDA Annual Reports (Periodic Adverse Event reports) were reviewed covering 3 separate NDA's (20-235, 7 reports; 20-882, 14 reports; 21-129, 8 reports). In addition, 1 Annual Report for NDA 20-235 was found. It was not possible to obtain a full complement of all Annual (or Quarterly, depending on approval date) Reports for every NDA and IND designation in the provided database.

169. The NDA Report data demonstrate signals related to suicide events and to which Pfizer Defendants should have responded. These include a 4-fold increase in suicide attempts from 1998 to 1999 and a doubling of suicide attempts from 2000 to 2001. In addition, the number of intentional overdoses showed increases from 1999 through 2002.

170. In addition, other adverse psychobiologic events were found in Pfizer Defendants' NDA Periodic and Adverse Event Reports. Comparing data reported in 1998 to those reported in 2002 (for NDA 20-235), significant increases in the number of reports of thinking abnormal, depression, anxiety, emotional lability and agitation are observed. These events further implicate gabapentin in a battery of psychobiologic adverse events and demonstrate that action should have been taken to strengthen the product labeling to warn patients of the risks associated with gabapentin.

NDA Annual Report Documents

NDA #	Date Range Reviewed	# Reports*	Description
20-235	10/1/96 – 8/18/02	7	Quarterly (1) + Annual Reports
20-882	10/1/98 – 8/18/02	14	Quarterly + Annual (1) Reports
21-129	3/1/00 – 5/31/02	8	Quarterly Reports

* Periodic Adverse Event Reports (1 Annual Report was also reviewed)

NDA Periodic Adverse Event Reports

NDA 20-235

Suicide-Related Adverse Events

Event	**10/1/96-12/31/96**	**1/1/97-12/31/97[&]**	**1/1/98-12/31/98**	**1/1/99-12/31/99**	**1/1/00-12/31/00**	**1/1/01-12/31/01**	**1/1/02-8/18/02**
Intentional Injury	**0**[#]	-	**1** (0)*	**0**	**0**	**0**	**0**
Intentional Overdose	**0**	-	**0**	**3** (3)	**23** (7)	**61** (12)	**177** (61)
Suicidal Ideation	**0**	-	**0**	**0**	**0**	**0**	**3** (3)
Suicide Attempt	**0**	-	**1** (1)	**4** (3)	**4** (4)	**8** (7)	**2** (1)
Death by Suicide	**0**	-	**0**	**0**	**0**	**0**	**1** (1)

[&] This Periodic Adverse Event Report was not found
[#] Total number of events presented in **bold** type
[*] Numbers in parentheses denote events coded as serious.

NDA 20-882

Suicide-Related Adverse Events

Event	10/1/98-12/31/98	1/1/99- 12/31/99[+]	1/1/00- 12/31/00[+]	1/1/01-9/30/01[+]	10/1/01-8/18/02
Intentional Injury	**0**[#]	**0**	**0**	**0**	**0**
Intentional Overdose	**0**	**0**	**1** (0)*	**2** (0)	**14** (5)
Suicidal Ideation	**0**	**0**	**0**	**0**	**0**
Suicide Attempt	**0**	**0**	**0**	**0**	**0**
Death by Suicide	**0**	**0**	**0**	**0**	**0**

[+] Combined Quarterly Reports

[#] Total number of events presented in **bold** type

* Numbers in parentheses denote events coded as serious

NDA 21-129

Suicide-Related Adverse Events

There were no reports of Intentional injury, Intentional overdose, Suicidal ideation, Suicide attempt, or death by suicide contained in Periodic Adverse Event Reports prepared under NDA 21-129 for the period March 1, 2000 through May 31, 2002.

NDA Periodic Adverse Event Reports

NDA 20-235

Psychobiologic Adverse Events

Event	10/1/96-12/31/96	1/1/97-12/31/97[&]	1/1/98-12/31/98	1/1/99-12/31/99	1/1/00-12/31/00	1/1/01-12/31/01	1/1/02-8/18/02
Thinking Abnormal	**6**[#] (0)*	-	**26** (1)	**30** (4)	**57** (7)	**52** (10)	**53** (2)
Confusion	**1** (1)	-	**28** (4)	**31** (4)	**37** (2)	**59** (22)	**37** (8)
Depression	**2** (0)	-	**20** (6)	**19** (3)	**29** (0)	**52** (11)	**41** (5)
Anxiety	**3** (0)	-	**20** (2)	**25** (2)	**30** (2)	**46** (6)	**29** (1)
Nervousness	**1** (0)	-	**24** (0)	**22** (2)	**23** (2)	**33** (1)	**14** (0)
Emotional Lability	**1** (0)	-	**7** (1)	**14** (0)	**17** (1)	**21** (1)	**24** (0)
Hostility	**4** (0)	-	**13** (2)	**19** (0)	**14** (2)	**24** (2)	**16** (2)
Depersonalization	**1** (0)	-	**14** (0)	**8** (0)	**7** (0)	**26** (0)	**21** (0)
Personality Disorder	**2** (0)	-	**9** (3)	**19** (5)	**17** (2)	**15** (2)	**3** (0)
Hallucinations	**1** (0)	-	**10** (0)	**16** (4)	**0**	**15** (8)	**16** (5)
Agitation	**1** (0)	-	**2** (0)	**11** (2)	**7** (0)	**8** (2)	**25** (1)
Abnormal Dreams	**2** (0)	-	**3** (1)	**7** (0)	**10** (0)	**9** (1)	**3** (1)
Psychosis	**1** (0)	-	**4** (1)	**5** (3)	**6** (2)	**11** (4)	**6** (2)
Manic Reaction	**0**	-	**4** (1)	**9** (0)	**5** (3)	**13** (2)	**1** (1)
Euphoria	**1** (0)	-	**4** (0)	**5** (0)	**4** (0)	**4** (1)	**3** (0)
Paranoid Reaction	**1** (0)	-	**2** (0)	**2** (0)	**4** (0)	**9** (3)	**4** (4)
Apathy	**0**	-	**0**	**0**	**2** (1)	**6** (0)	**3** (0)
Manic Depressive Reaction	**0**	-	**1** (0)	**2** (2)	**0**	**2** (1)	**6** (0)

[&] Unable to locate this Periodic Adverse Event Report
[#] Total number of events presented in **bold** type
* Numbers in parentheses denote events coded as serious.

NDA Periodic Adverse Event Reports (*continued*)

NDA 20-882

Psychobiologic Adverse Events

Event	**10/1/98-12/31/98**	**1/1/99-12/31/99**[+]	**1/1/00-12/31/00**[+]	**1/1/01-9/30/01**[+]	**10/1/01-8/18/02**
Depression	**0**[#]	**0**	**2** (0)*	**1** (0)	**3** (0)
Anxiety	**0**	**0**	**0**	**1** (0)	**4** (0)
Agitation	**0**	**0**	**0**	**0**	**4** (0)
Depersonalization	**0**	**0**	**0**	**1** (0)	**2** (0)
Emotional Lability	**0**	**0**	**1** (0)	**0**	**2** (0)
Nervousness	**0**	**0**	**1** (0)	**1** (0)	**1** (0)
Confusion	**0**	**0**	**1** (0)	**0**	**1** (0)
Thinking Abnormal	**0**	**0**	**0**	**0**	**2** (0)
Hallucinations	**0**	**0**	**0**	**0**	**1** (1)
Hostility	**0**	**0**	**1** (0)	**0**	**0**
Personality Disorder	**0**	**0**	**0**	**0**	**1** (0)

[+] Combined Quarterly Reports

[#] Total number of events presented in **bold** type

[*] Numbers in parentheses denote events coded as serious

NDA Periodic Adverse Event Reports (*continued*)

NDA 21-129

Psychobiologic Adverse Events

Event	**3/1/00-8/31/00**[+]	**12/1/00-11/30/01**[+]	**12/1/01-5/31/02**[+]
Anxiety	**0**[#]	**1** (0)*	**0**
Depression	**0**	**1** (0)	**0**
Emotional Lability	**0**	**1** (0)	**0**
Nervousness	**0**	**1** (0)	**0**
Personality Disorder	**0**	**1** (0)	**0**

+ Combined Quarterly Reports

[#] Total number of events presented in **bold** type

* Numbers in parentheses denote events coded as serious

INVESTIGATIONAL NEW DRUG (IND) ANNUAL REPORTS

171. This section provides an overview of adverse psychobiologic effects found in IND Annual Reports. Annual Reports were found for 5 separate INDs: 28,454 (6 reports); 52,719 (4 reports); 57,813 (3 reports); 60,622 (2 reports); and 63,994 (1 report). For IND reports, an overview of these events leading to withdrawal from clinical trials and a summary of all serious psychobiologic adverse events are provided.

172. Suicide events were reported in the Annual Reports. One "completed suicide" and one instance of "suicidal" are noted, neither of which were considered related to gabapentin. Two instances of "suicidal ideation" were reported as being unlikely related to gabapentin. The one "suicide attempt" reported was definitely related to gabapentin. There were 2 suicide-related events (suicidal and suicidal ideation) in patients not receiving gabapentin. In addition, one patient committed suicide (the event was considered not related to study medication) but insufficient information was provided to determine whether this patient was taking gabapentin or placebo.

IND Annual Reports

IND #	Date Range Received	Total # Reports	Description
28,454	7/2/96 - 8/18/02	6	Annual Reports
52,719	2/21/98 – 8/18/02	4	Annual Reports (Missing 3/17/99 – 12/19/99)
57,813	12/8/99 – 8/18/02	3	Annual Reports
60,622	5/2/00 – 8/18/02	2	Annual Reports (Missing 5/2/01 – 7/16/01)
63,994	2/17/02 – 8/18/02	1	Annual Report

IND Annual Reports

Suicide-Related Adverse Events

Event	IND	Treatment	Annual Report Date Range
Intentional Overdose	28,454	GBP 2700 mg/day	7/1/97-7/1/98
Intentional Overdose	Unknown*	GBP 4500 mg/day	5/2/00-5/1/01
Suicidal Ideation[#]	28,454	No Treatment	7/1/97-7/1/98
Suicidal Ideation	28,454	GBP 34.4 mg/kg	7/2/98-5/1/99
Suicide Attempt	Unknown	GBP 4500 mg/day	5/2/00-5/1/01
Suicide	28,454	Blinded	7/1/97-7/1/98

*The 2001-2002 Annual Report for gabapentin includes data from 4 separate INDs but does not specify under which IND the adverse event originated.

[#] This patient experienced suicidal ideation prior to being randomized to treatment.

173. Data provided below include information on withdrawals due to psychobiologic adverse events (Section A) and serious psychobiologic adverse events (Section B). These data are separated by year. Of note, patients taking gabapentin withdrew due to a variety of psychobiologic adverse events, including emotional lability (7 patients) and hostility (3 patients). A constellation of serious psychobiologic adverse events was also observed including reports of mania, hostility and agitation. These types of events mirrored those observed in post-marketing adverse event databases and were further evidence of the growing numbers of psychobiologic adverse events occurring in gabapentin patients.

Gabapentin Annual IND Reports

1996-1997

A. Withdrawals

Event (Frequency)	Treatment	IND #
Emotional Lability (5)	Gabapentin	28,454
Acute Mania (2)	Gabapentin	28,454
Acute Mania (2)	Placebo	28,454
Depression (3)	Placebo	28,454
Dysphoric Mania (3)	Placebo	28,454
Hostility (3)	Gabapentin	28,454
Psychosis (2)	Gabapentin	28,454
Psychosis (1)	Placebo	28,454
Thinking Abnormal (2)	Gabapentin	28,454
Confusion (2)	Gabapentin	28,454
Nervousness (1)	Gabapentin	28,454
Nervousness (1)	Placebo	28,454
Anxiety (1)	Gabapentin	28,454
Anxiety (1)	Placebo	28,454
Agitation (1)	Gabapentin	28,454
Personality Disorder (1)	Gabapentin	28,454
Emotionally Upset (1)	Placebo	28,454
Manic Psychosis (1)	Placebo	28,454
Mania (1)	Placebo	28,454

1996-1997

B. Serious Adverse Events

Event (Frequency)	Treatment	IND #
Mania (2)	Gabapentin	28,454
Mania (4)	Placebo	28,454
Psychosis (1)	Gabapentin	28,454
Psychosis (2)	Placebo	28,454
Agitation (2)	Gabapentin	28,454
Depression (1)	Placebo	28,454
Hostility (1)	Gabapentin	28,454
Overdose (1)	Gabapentin	28,454
Suicidal (1)	Placebo	28,454

1997-1998

A. Withdrawals

Event (Frequency)	Treatment	IND #
Thinking Abnormal (3)	Gabapentin	28,454, 52,719
Thinking Abnormal (2)	Placebo	28,454, 52,719
Thinking Abnormal (1)	Unknown	52,719
Manic Reaction (4)	Placebo	28,454
Emotional Lability (2)	Gabapentin	28,454
Confusion (1)	Gabapentin	52,719
Confusion (1)	Placebo	28,454
Anxiety (1)	Gabapentin	52,719
Personality Disorder (1)	Gabapentin	52,719

1997-1998

B. Serious Adverse Events

Event (Frequency)	Treatment	IND #
Depression (2)	Gabapentin	28,454
Overdose (1)	Gabapentin	28,454
Overdose (1)	Placebo	28,454
Overdose (intentional) (1)	Gabapentin	28,454
Anxiety (1)	Gabapentin	28,454
Psychotic Episode (1)	Gabapentin	28,454
Acute Mania with Psychotic Features (1)	Placebo	28,454
Dysphoric Mania (1)	Placebo	28,454
Suicidal Ideation (1)	Placebo	28,454
Suicide (1)	Blinded	28,454

1998-1999

A. Withdrawals

Event (Frequency)	Treatment	IND #
Thinking Abnormal (1)	Gabapentin	52,719

B. Serious Adverse Events

Event (Frequency)	Treatment	IND #
Explosive Aggressive Behavior (1)	Gabapentin	28,454
Suicide Ideation (1)	Gabapentin	28,454
Overdose (1)	Placebo	28,454

1999-2000

A. Withdrawals

No withdrawals due to psychobiologic adverse events

B. Serious Adverse Events

No Serious Psychobiologic Adverse Events reported

2000-2001

A. Withdrawals

Event	Treatment	IND #
Aggressive Behavior (1)	Gabapentin	57,813
Behavior Change (1)	Gabapentin	57,813
Behavior Problems (1)	Gabapentin	57,813
Severe Irritability (1)	Gabapentin	57,813
Anxiousness (1)	Placebo	60,622

B. Serious Adverse Events

Event (Frequency)	Treatment	IND #
Intentional Overdose (1)	Gabapentin	Unknown
Suicide Attempt (1)	Gabapentin	Unknown

2001-2002

A. Withdrawals

Event (Frequency)	Treatment	IND #
Confusion (1)	Gabapentin	63,994
Emotional Lability (1)	Gabapentin	57,813
Hostility (1)	Gabapentin	57,813
Nervousness (1)	Gabapentin	57,813

B. Serious Adverse Events

Event (Frequency)	Treatment	IND #
Agitation (2)	Gabapentin	28,454
Confusion (1)	Gabapentin	63,994

SPONTANEOUS REPORTING SYSTEM (SRS) / ADVERSE EVENT REPORTING SYSTEM (AERS)

174. Adverse psychobiologic events occurring in individuals receiving gabapentin and reported to the Spontaneous Reporting System (SRS) / Adverse Event Reporting System (AERS) database were analyzed. A number of signals associated with suicide-related events were apparent during the time period reviewed. These include a significant number of cumulative suicide attempts in 1996 (8 reports) and a steady increase thereafter. By the end of 2002, this number had increased to 73 reports. In a similar manner, suicide ideation reports steadily increased from 1 event (through the end of 1997) to 15 events in 1999. At the end of 2002, 55 reports were found in the database. Completed suicides began to appear in the database in 1999 (3 reports) and by 2002, the number of reports had increased by a factor of 9 (to 27).

175. Notable increases were also observed in the SRS/AERS database for the numbers of aggression, anxiety, agitation, depersonalization and depression events from 1996 to 2002. These events, coupled with the suicide-related events and the constellation of other adverse psychobiologic events found in the SRS/AERS database, should have alerted Pfizer Defendants to the serious risks associated with gabapentin and prompted them to perform necessary amplifications of the gabapentin product labeling. This was particularly important during the period under review as gabapentin was being used increasingly for indications for which it was not approved, including for a number of mood disorders. These patient populations are obviously considered more at risk for suicide-related events.[61] As such, a full explanation of the (purported) benefits and risks associated with the uses of gabapentin should have been given to these patients.

[61] Khan *et al.*, 2002.

Suicide-related events from the SRS/AERS Database (1996-2002)

	1996 Q4		1997 Q4		1998 Q4		1999 Q4		2000 Q4		2001 Q4		2002 Q4	
Costart Term	**Reports[#]**	**%**	**Reports**	**%**	**Reports**	**%**	**Reports**	**%**	**Reports**	**%**	**Reports**	**%**	**Reports**	**%**
Completed suicide							**3**	**0.12**	**8**	**0.21**	**22**	**0.39**	**27**	**0.42**
Suicide attempt	**8**	**1.21**	**10**	**1.16**	**12**	**0.84**	**25**	**1.02**	**43**	**1.14**	**63**	**1.10**	**73**	**1.13**
Suicidal ideation			**1**	**0.12**	**3**	**0.21**	**15**	**0.61**	**29**	**0.77**	**44**	**0.77**	**55**	**0.85**

[#]Reports are cumulative and represent numbers received through the fourth quarter for each year.

Psychobiologic Adverse Events from the SRS/AERS Database (1996-1999)

Gabapentin AERS / SRS Psychobiologic Adverse Event Data (1996 – 1999)

	1996 Q4		1997 Q4		1998 Q4		1999 Q4	
Costart Term	**Reports***	**Pct**	**Reports**	**Pct**	**Reports**	**Pct**	**Reports**	**Pct**
Abnormal Dreams	1	0.15%	1	0.12%	2	0.14%	4	0.16%
Affect lability	4	0.60%	6	0.69%	6	0.42%	6	0.25%
Aggression					3	0.21%	18	0.74%
Agitation	8	1.21%	10	1.16%	14	0.99%	33	1.35%
Anxiety	4	0.60%	4	0.46%	10	0.70%	28	1.15%
Completed suicide							**3**	**0.12%**
Confusional state	18	2.72%	26	3.01%	44	3.10%	83	3.40%
Delirium	3	0.45%	6	0.69%	12	0.84%	18	0.74%
Delusion	1	0.15%	1	0.12%	2	0.14%	4	0.16%
Depersonalization	1	0.15%	1	0.12%	3	0.21%	7	0.29%
Depression	10	1.51%	11	1.27%	25	1.76%	51	2.09%
Hallucination	10	1.51%	15	1.73%	24	1.69%	35	1.43%
Hostility	15	2.27%	18	2.08%	22	1.55%	27	1.11%
Intentional self-injury								
Major depression	2	0.30%	2	0.23%	2	0.14%	5	0.20%
Nervousness	5	0.76%	6	0.69%	14	0.99%	23	0.94%
Overdose	10	1.51%	16	1.85%	23	1.62%	37	1.51%
Paranoia	4	0.60%	5	0.58%	7	0.49%	8	0.33%
Personality disorder	7	1.06%	7	0.81%	9	0.63%	13	0.53%
Psychotic disorder	12	1.81%	12	1.39%	21	1.48%	29	1.19%
Suicidal ideation			**1**	**0.12%**	**3**	**0.21%**	**15**	**0.61%**
Suicide attempt	**8**	**1.21%**	**10**	**1.16%**	**12**	**0.84%**	**25**	**1.02%**
Thinking abnormal	9	1.36%	11	1.27%	13	0.91%	22	0.90%
Death	18	2.72%	18	2.08%	21	1.48%	26	1.06%

* Numbers represent cumulative reports

Psychobiologic Adverse Events from the SRS/AERS Database (2000-2002)

Gabapentin AERS Psychobiologic Adverse Event Data (2000 – 2002)						
	2000 Q4		2001 Q4		2002 Q4	
Costart Term	**Reports***	**Pct**	**Reports**	**Pct**	**Reports**	**Pct**
Abnormal Dreams	10	0.26%	13	0.23%	13	0.20%
Affect lability	6	0.16%	6	0.11%	6	0.09%
Aggression	24	0.63%	37	0.65%	45	0.70%
Agitation	48	1.27%	68	1.19%	81	1.26%
Anxiety	53	1.40%	92	1.61%	117	1.82%
Apathy	3	0.08%	5	0.09%	5	0.08%
Completed suicide	**8**	**0.21%**	**22**	**0.39%**	**27**	**0.42%**
Confusional state	132	3.49%	205	3.59%	246	3.82%
Delirium	24	0.63%	35	0.61%	41	0.64%
Delusion	11	0.29%	15	0.26%	18	0.28%
Depersonalization	9	0.24%	12	0.21%	12	0.19%
Depression	92	2.43%	145	2.54%	186	2.89%
Hallucination	52	1.37%	76	1.33%	86	1.33%
Hostility	33	0.87%	39	0.68%	40	0.62%
Intentional self-injury	2	0.05%	3	0.05%	4	0.01%
Major depression	7	0.18%	9	0.16%	9	0.14%
Nervousness	40	1.06%	56	0.98%	58	0.90%
Overdose	62	1.64%	96	1.68%	130	2.02%
Paranoia	14	0.37%	25	0.44%	26	0.40%
Personality disorder	13	0.34%	13	0.23%	13	0.20%
Psychotic disorder	39	1.03%	55	0.96%	66	1.02%
Suicidal ideation	**29**	**0.77%**	**44**	**0.77%**	**55**	**0.85%**
Suicide attempt	**43**	**1.14%**	**63**	**1.10%**	**73**	**1.13%**
Thinking abnormal	26	0.69%	41	0.72%	46	0.71%
Death	32	0.85%	60	1.05%	93	1.44%

* Numbers represent cumulative reports

PFIZER DEFENDANTS' INTERNAL ADVERSE EVENT DATABASE

176. The internal adverse event database compiled by Pfizer Defendants to monitor adverse events reported to the company through various sources was reviewed. A review of the top 25 adverse events reported to this internal database (from 1996 through 2002) reveals a large number of intentional overdose events. Although some of these events may also include off-label use of a higher than approved dose of gabapentin, Pfizer Defendants also knew of suicide attempts from clinical trials (reviewed in previous sections of this report) and another safety alert database contained significant numbers of suicide attempts by 1997 (SRS/AERS). Thus, they had a responsibility to incorporate stronger self-injury, suicide-related warnings into the gabapentin labeling. In addition, depression ranks consistently in the top 10 events from 1996 through 1999.

177. Pfizer Defendants did update the gabapentin product label in 1997 to include the following terms under the heading **Post-introduction Reports**: erythema multiforme, Stevens Johnson Syndrome and elevated liver function tests. In the Pfizer Defendants internal database at the end of 1997, there were 3 reports of erythema multiforme, 4 reports of Stevens Johnson Syndrome and 6 reports of liver function tests abnormal. In contrast, there were 7 reports of suicidal ideation, 5 reports of suicide attempt and 1 report of a completed suicide. Why Pfizer Defendants chose to focus only on these adverse events and ignore other life-threatening and even fatal adverse events is concerning.

178. In 1998, the **Post-introduction Reports** section of the gabapentin labeling was replaced with a section titled **Postmarketing and Other Experience.** The following terms were added, following an examination of the Pfizer Defendants internal database, to those already present in the previous label (note that the number of cumulative reports present in the Pfizer Defendants internal database is provided in parentheses): angioedema (1), blood glucose fluctuation (0), fever (0), and jaundice (3). A review of this database revealed that similar label changes should have been made for suicide-related events during this same time period. The corresponding numbers for suicide attempt and suicidal ideation in Pfizer's internal database during this time were 7 and 11.

179. This particular label change represented yet another opportunity for Pfizer Defendants to update their gabapentin product labeling to warn patients and prescribers of the risks associated with this product. The presence of the terms "suicidal" and "suicide gesture" under adverse events observed in clinical trials did not (and does not) adequately inform patients of the postmarketing risks associated with gabapentin use.[62] At a minimum, these suicide-related terms should have been included in the Post-marketing and Other Experience section of the label. These analyses were corroborated on May 3, 2006, when FDA approved a labeling supplement noting reports of suicide attempts and completed suicide in patients taking gabapentin in clinical trials.[63]

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[62] As previously set forth in this report, in the absence of the product labeling specifically referencing "suicide" and "suicide attempt", these adverse events are to be considered unexpected and unlabeled. *See* 21 CFR 314.80(a): "Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity." For example, "Suicide attempt" is a term more specific --- and arguably even of greater severity --- than "suicidal" or "suicidal gesture". Prior to the 2005/2006 labeling change, Pfizer Defendants submitted suicide reports as unlabeled adverse events.

[63] *See* Correspondence dated May 3, 2006 from Russel Katz, MD (FDA, Dir. of Neurology Products CDER). The correspondences approved the "Changes Being Effected" supplemental new drug applications that "provide[d] for revisions of suicide-related adverse event terms under the subheading **Other Adverse Events Observed During All Clinical Trials** and an update to the number of patients exposed to Neurontin in add-on Epilepsy trials."

Intentional Overdose Events Reported to Pfizer Defendants' Internal Database (1996-2002)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Intentional overdose	1996-Q4	0	14	915	1.53%
Intentional overdose	1997-Q4	2	17	1064	1.60%
Intentional overdose	1998-Q4	2	25	1246	2.01%
Intentional overdose	1999-Q4	3	32	1526	2.10%
Intentional overdose	2000-Q4	5	52	1924	2.70%
Intentional overdose	2001-Q4	25	130	2638	4.93%
Intentional overdose	2002-Q4	33	291	3604	8.07%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (1996 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Convulsion	1996-Q4	11	174	915	19.02%
Status epilepticus	1996-Q4	1	50	915	5.46%
Death	1996-Q4	0	48	915	5.25%
Somnolence	1996-Q4	4	33	915	3.61%
Ataxia	1996-Q4	1	27	915	2.95%
Depression	1996-Q4	0	25	915	2.73%
Pneumonia	1996-Q4	1	24	915	2.62%
Grand mal convulsion	1996-Q4	0	21	915	2.30%
Psychotic disorder	1996-Q4	0	21	915	2.30%
Sudden death	1996-Q4	1	20	915	2.19%
Dizziness	1996-Q4	1	19	915	2.08%
Drug interaction	1996-Q4	1	19	915	2.08%
Vomiting	1996-Q4	3	19	915	2.08%
Aggression	1996-Q4	2	18	915	1.97%
Confusional state	1996-Q4	1	18	915	1.97%
Anticonvulsant drug level increased	1996-Q4	1	16	915	1.75%
Pyrexia	1996-Q4	0	16	915	1.75%
Lethargy	1996-Q4	1	15	915	1.64%
Agitation	1996-Q4	1	14	915	1.53%
Fall	1996-Q4	1	14	915	1.53%
Intentional overdose	1996-Q4	0	14	915	1.53%
Pancreatitis	1996-Q4	2	12	915	1.31%
Abdominal pain	1996-Q4	1	11	915	1.20%
Tremor	1996-Q4	0	11	915	1.20%
Cerebrovascular accident	1996-Q4	0	10	915	1.09%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (1997 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Convulsion	1997-Q4	4	192	1064	18.05%
Adverse event	1997-Q4	13	51	1064	4.79%
Status epilepticus	1997-Q4	0	51	1064	4.79%
Death	1997-Q4	0	49	1064	4.61%
Somnolence	1997-Q4	1	37	1064	3.48%
Ataxia	1997-Q4	1	31	1064	2.91%
Pneumonia	1997-Q4	1	29	1064	2.73%
Drug interaction	1997-Q4	0	27	1064	2.54%
Depression	1997-Q4	0	25	1064	2.35%
Dizziness	1997-Q4	1	24	1064	2.26%
Vomiting	1997-Q4	0	24	1064	2.26%
Psychotic disorder	1997-Q4	0	23	1064	2.16%
Confusional state	1997-Q4	0	22	1064	2.07%
Sudden death	1997-Q4	0	22	1064	2.07%
Grand mal convulsion	1997-Q4	0	21	1064	1.97%
Pyrexia	1997-Q4	1	20	1064	1.88%
Lethargy	1997-Q4	1	19	1064	1.79%
Aggression	1997-Q4	0	18	1064	1.69%
Fall	1997-Q4	1	17	1064	1.60%
Intentional overdose	1997-Q4	2	17	1064	1.60%
Anticonvulsant drug level increased	1997-Q4	0	16	1064	1.50%
Agitation	1997-Q4	0	15	1064	1.41%
Headache	1997-Q4	1	14	1064	1.32%
Abdominal pain	1997-Q4	0	13	1064	1.22%
Dyspnoea	1997-Q4	0	13	1064	1.22%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (1998 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Convulsion	1998-Q4	5	209	1246	16.77%
Adverse event	1998-Q4	21	135	1246	10.83%
Death	1998-Q4	2	53	1246	4.25%
Status epilepticus	1998-Q4	0	53	1246	4.25%
Somnolence	1998-Q4	2	41	1246	3.29%
Ataxia	1998-Q4	0	35	1246	2.81%
Drug interaction	1998-Q4	3	34	1246	2.73%
Pneumonia	1998-Q4	0	34	1246	2.73%
Depression	1998-Q4	1	29	1246	2.33%
Dizziness	1998-Q4	4	29	1246	2.33%
Confusional state	1998-Q4	1	28	1246	2.25%
Intentional overdose	1998-Q4	2	25	1246	2.01%
Psychotic disorder	1998-Q4	1	25	1246	2.01%
Vomiting	1998-Q4	1	25	1246	2.01%
Pyrexia	1998-Q4	1	24	1246	1.93%
Sudden death	1998-Q4	0	24	1246	1.93%
Grand mal convulsion	1998-Q4	0	22	1246	1.77%
Headache	1998-Q4	4	21	1246	1.69%
Lethargy	1998-Q4	1	21	1246	1.69%
Aggression	1998-Q4	1	19	1246	1.52%
Fall	1998-Q4	0	19	1246	1.52%
Anticonvulsant drug level increased	1998-Q4	1	17	1246	1.36%
Pancreatitis	1998-Q4	1	17	1246	1.36%
Asthenia	1998-Q4	1	16	1246	1.28%
Dyspnoea	1998-Q4	0	16	1246	1.28%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (1999 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Adverse event	1999-Q4	48	283	1526	18.55%
Convulsion	1999-Q4	12	245	1526	16.06%
Drug interaction	1999-Q4	11	70	1526	4.59%
Death	1999-Q4	3	61	1526	4.00%
Status epilepticus	1999-Q4	1	56	1526	3.67%
Somnolence	1999-Q4	3	51	1526	3.34%
Pneumonia	1999-Q4	2	43	1526	2.82%
Ataxia	1999-Q4	3	41	1526	2.69%
Confusional state	1999-Q4	1	39	1526	2.56%
Depression	1999-Q4	1	37	1526	2.42%
Dizziness	1999-Q4	2	36	1526	2.36%
Vomiting	1999-Q4	1	34	1526	2.23%
Pyrexia	1999-Q4	3	33	1526	2.16%
Intentional overdose	1999-Q4	3	32	1526	2.10%
Psychotic disorder	1999-Q4	2	30	1526	1.97%
Headache	1999-Q4	2	27	1526	1.77%
Fall	1999-Q4	4	26	1526	1.70%
Grand mal convulsion	1999-Q4	0	24	1526	1.57%
Sudden death	1999-Q4	0	24	1526	1.57%
Lethargy	1999-Q4	1	23	1526	1.51%
Pancreatitis	1999-Q4	1	23	1526	1.51%
Tremor	1999-Q4	3	23	1526	1.51%
Vision blurred	1999-Q4	4	23	1526	1.51%
Abdominal pain	1999-Q4	0	22	1526	1.44%
Aggression	1999-Q4	1	21	1526	1.38%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (2000 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Adverse event	2000-Q4	60	485	1924	25.21%
Convulsion	2000-Q4	6	285	1924	14.81%
Drug interaction	2000-Q4	9	99	1924	5.15%
Death	2000-Q4	11	76	1924	3.95%
Somnolence	2000-Q4	3	65	1924	3.38%
Dizziness	2000-Q4	13	62	1924	3.22%
Status epilepticus	2000-Q4	1	57	1924	2.96%
Pneumonia	2000-Q4	4	54	1924	2.81%
Confusional state	2000-Q4	2	52	1924	2.70%
Intentional overdose	2000-Q4	5	52	1924	2.70%
Ataxia	2000-Q4	1	49	1924	2.55%
Vomiting	2000-Q4	2	48	1924	2.49%
Depression	2000-Q4	5	47	1924	2.44%
Fall	2000-Q4	7	42	1924	2.18%
Pyrexia	2000-Q4	1	41	1924	2.13%
Headache	2000-Q4	9	40	1924	2.08%
Tremor	2000-Q4	8	40	1924	2.08%
Psychotic disorder	2000-Q4	1	36	1924	1.87%
Fatigue	2000-Q4	4	31	1924	1.61%
Vision blurred	2000-Q4	4	30	1924	1.56%
Asthenia	2000-Q4	2	29	1924	1.51%
Abdominal pain	2000-Q4	3	28	1924	1.46%
Pancreatitis	2000-Q4	2	28	1924	1.46%
Sudden death	2000-Q4	1	28	1924	1.46%
Weight increased	2000-Q4	2	27	1924	1.40%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (2001 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Adverse event	2001-Q4	14	586	2638	22.21%
Convulsion	2001-Q4	15	360	2638	13.65%
Intentional overdose	2001-Q4	25	130	2638	4.93%
Drug interaction	2001-Q4	4	126	2638	4.78%
Death	2001-Q4	12	110	2638	4.17%
Dizziness	2001-Q4	10	105	2638	3.98%
Somnolence	2001-Q4	12	104	2638	3.94%
Confusional state	2001-Q4	9	91	2638	3.45%
Pneumonia	2001-Q4	5	86	2638	3.26%
Depression	2001-Q4	4	74	2638	2.81%
Vomiting	2001-Q4	4	71	2638	2.69%
Fall	2001-Q4	12	70	2638	2.65%
Headache	2001-Q4	5	67	2638	2.54%
Tremor	2001-Q4	3	67	2638	2.54%
Unevaluable event	2001-Q4	7	66	2638	2.50%
Pyrexia	2001-Q4	3	62	2638	2.35%
Asthenia	2001-Q4	6	61	2638	2.31%
Fatigue	2001-Q4	3	60	2638	2.27%
Ataxia	2001-Q4	3	59	2638	2.24%
Status epilepticus	2001-Q4	2	59	2638	2.24%
Nausea	2001-Q4	8	54	2638	2.05%
Dyspnoea	2001-Q4	7	51	2638	1.93%
Pain	2001-Q4	9	51	2638	1.93%
Weight increased	2001-Q4	3	49	2638	1.86%
Medication error	2001-Q4	15	48	2638	1.82%

Top 25 Adverse Events Reported to Pfizer Defendants' Internal Database (2002 Q4)

Term	Date	Reports	Cumulative Reports	Cumulative Total	Pct
Adverse event	2002-Q4	2	633	3604	17.56%
Convulsion	2002-Q4	10	443	3604	12.29%
Intentional overdose	2002-Q4	33	291	3604	8.07%
Dizziness	2002-Q4	18	182	3604	5.05%
Medication error	2002-Q4	31	171	3604	4.74%
Drug interaction	2002-Q4	10	167	3604	4.63%
Somnolence	2002-Q4	16	163	3604	4.52%
Death	2002-Q4	10	154	3604	4.27%
Pain	2002-Q4	21	130	3604	3.61%
Unevaluable event	2002-Q4	2	125	3604	3.47%
Confusional state	2002-Q4	9	123	3604	3.41%
Depression	2002-Q4	11	119	3604	3.30%
Headache	2002-Q4	11	107	3604	2.97%
Fatigue	2002-Q4	15	106	3604	2.94%
Pneumonia	2002-Q4	6	102	3604	2.83%
Asthenia	2002-Q4	9	100	3604	2.77%
Fall	2002-Q4	5	100	3604	2.77%
Tremor	2002-Q4	5	97	3604	2.69%
Weight increased	2002-Q4	9	95	3604	2.64%
Vomiting	2002-Q4	5	94	3604	2.61%
Nausea	2002-Q4	9	87	3604	2.41%
Ataxia	2002-Q4	6	75	3604	2.08%
Pyrexia	2002-Q4	2	75	3604	2.08%
Dyspnoea	2002-Q4	4	71	3604	1.97%
Cerebrovascular accident	2002-Q4	8	70	3604	1.94%

Pfizer Defendants' Internal Adverse Event Database - A Comparison of Events Added to the Label Versus *Suicide-Related* Terms

1996 Q4

Adverse Event	Date	Reports	Cumulative Reports	Cumulative Total	Pct.
Intentional overdose	1996-Q4	0	14	915	1.53%
Suicide Attempt	1996-Q4	0	5	915	0.55%
Suicide Ideation	1996-Q4	0	7	915	0.77%
Erythema Multiforme*	1996-Q4	0	3	915	0.33%
Stevens Johnson Syndrome*	1996-Q4	0	3	915	0.33%
Liver function test abnormal*#	1996-Q4	0	4	915	0.44%

@Suicide-related terms (*italicized*) were not added to the gabapentin label in 1997

*Added to the gabapentin label January 1997

Actual term added was elevated liver function tests

1997 Q4

Adverse Event	Date	Reports	Cumulative Reports	Cumulative Total	Pct.
Intentional overdose	1997-Q4	2	17	1064	1.60%
Suicide Attempt	1997-Q4	0	5	1064	0.47%
Suicide Ideation	1997-Q4	0	7	1064	0.66%
Angioneurotic edema&+	1997-Q4	0	1	1064	0.09%
Blood Glucose Fluctuations&	1997-Q4	0	0	1064	0.00%
Erythema Multiforme*	1997-Q4	0	3	1064	0.28%
Fever&	1997-Q4	0	0	1064	0.00%
Jaundice&	1997-Q4	0	3	1064	0.28%
Liver function test abnormal*#	1997-Q4	0	6	1064	0.56%
Stevens Johnson Syndrome*	1997-Q4	0	4	1064	0.37%

@Suicide-related terms (*italicized*) were not added to the gabapentin label in 1998

&Added to the gabapentin label February 1998

+Actual term added was angioedema

*Added to the gabapentin label January 1997

Actual term added was elevated liver function tests

World Health Organization (WHO) – Adverse Event Data

180. Adverse psychobiologic events associated with gabapentin and reported to the World Health Organization (WHO) between 1993 and 2005 were compiled. The table below lists (by year) the top 25 (annual) adverse psychobiologic events reported during this time period. Of note, "suicide attempt" was the third most frequently reported event with a total of 249 reports, 61 of which occurred during the 1996-2002 period. In addition, 28 reports of suicide attempt were reported in 2000 alone, compared to 3 reports (total) in the previous 6 years combined. Similar trends were noted for other psychobiologic events including depression and depersonalization, each of which was reported 49 times between 1996 and 2002. Interestingly, both depression and depersonalization events, considered a precursor to suicide-related behavior[64], spiked again in 2005.

181. This myriad of adverse psychobiologic events mirrors the elevated numbers observed in other adverse event databases (Pfizer Defendants' internal database, SRS/AERS) and confirms the association of gabapentin with psychobiologic events. Thus, these WHO data provide additional evidence of the necessity of gabapentin labeling changes related to adverse psychobiologic events, especially those related to suicidal behaviors.

[64] Kelly and Knudson, 2000

WORLD HEALTH ORGANIZATION
TOP 25 PSYCHIATRIC ADVERSE EVENTS 1993-2005

Adverse Reaction	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
SOMNOLENCE	0	21	46	10	32	7	10	103	43	37	56	41	90	496
CONFUSION	0	7	10	9	13	0	7	51	22	26	49	25	57	276
SUICIDE ATTEMPT*	***0***	***2***	***0***	***0***	***1***	***0***	***0***	***28***	***19***	***13***	***48***	***42***	***96***	***249***
AMNESIA	0	1	3	2	7	5	3	44	19	11	25	11	47	178
DEPRESSION	0	1	5	5	5	1	3	21	11	3	27	14	56	152
AGGRESSIVE REACTION	0	11	24	11	13	4	1	18	4	5	15	9	37	152
HALLUCINATION	0	6	12	4	3	1	6	26	15	8	23	13	27	144
DEPERSONALIZATION	0	3	1	2	6	0	2	25	9	5	10	17	62	142
INSOMNIA	0	2	5	2	6	0	2	26	8	6	20	16	40	133
ANXIETY	0	0	6	2	2	1	2	23	3	8	14	15	47	123
AGITATION	0	6	13	3	7	1	2	14	6	4	20	7	35	118
NERVOUSNESS	0	7	10	5	6	4	3	22	9	5	6	13	21	111
DRUG ABUSE	0	0	0	0	0	0	0	52	12	9	11	8	11	103
PERSONALITY DISORDER	0	2	15	4	6	2	1	11	2	3	4	10	34	94
EMOTIONAL LABILITY	0	2	8	3	3	1	0	12	4	6	13	12	22	86
THINKING ABNORMAL	0	2	7	3	4	1	1	7	1	7	12	8	13	66
PSYCHOSIS	0	7	7	2	2	0	1	8	2	3	8	5	19	64
ANOREXIA	0	0	4	3	1	0	3	11	3	4	9	2	23	63
IMPOTENCE	0	2	3	1	3	2	5	10	7	3	6	6	9	57
DRUG DEPENDENCE	0	0	0	0	1	0	0	2	2	5	13	7	20	50
CONCENTRATION IMPAIRED	0	0	0	1	0	2	0	11	8	0	4	8	13	47
MENTAL DEFICIENCY	0	0	0	0	0	0	0	12	15	5	3	3	5	43
SLEEP DISORDER	0	0	2	1	1	0	0	3	1	4	5	6	12	35
LIBIDO DECREASED	0	0	5	2	0	0	3	8	0	2	2	4	5	31
PARANOID REACTION	0	1	4	1	4	1	0	3	4	2	7	1	3	31

* Intentional Overdose was not included under this term until 2004

HEALTH CANADA DATABASE

182. Canadian postmarketing adverse event data were evaluated and are summarized below. It is alarming to note that self harm and suicide related events accounted for four percent of the Neurontin database. Interestingly, Neurontin was considered the suspect agent by the reporting medical contact in over 60% of these cases. Notwithstanding the accumulation of these adverse psychobiologic events, Pfizer Canada did not add suicide-related events to the post-marketing adverse event discussion included with the 2005 labeling revision of Neurontin. The table below provides an overview of the suicide-related adverse events observed in the Health Canada database. These data reinforce the significant numbers of suicide-related events observed in both the FDA AERS database and the Pfizer Defendants internal adverse event database. Please note that while many adverse psychobiologic adverse events found in the Canadian database occurred during the time period under reviewed for this section of the report (*e.g.*, October 1996 through May 2002), almost all of the suicide-related events fall outside of this period. These suicide-related events are included as evidence that significant numbers of these types of events occur in other countries and that the trend continued through 2005.

183. In addition, other events believed to be precursors to self injurious behavior, including depersonalization, aggression, aggravated depression, agitation, aggravated psychosis and abnormal thoughts can be found in the Canadian database. These events are also absent from the Post-Marketing experience section of the Canadian professional labeling for gabapentin.

Health Canada Adverse Drug Reaction Database - Neurontin Suicide-Related Adverse Events

Report ID	Event Date	Event	Gabapentin Suspect Status	Serious/ Not Serious
177121	Apr-02	Suicidal Tendency	Concomitant	Serious
154637	Sep-02	Thoughts of Self Harm	Suspected	Serious
161362	Feb-03	Suicide Attempt	Suspected	Serious
164720	Apr-03	Suicidal Tendency	Concomitant	Serious
174648	Jul-04	Suicide Attempt	Suspected	Serious
174654	Jul-04	Suicide Attempt	Suspected	Serious
175100	Jul-04	Suicide Attempt	Suspected	Serious
177221	Aug-04	Suicide Attempt	Suspected	Serious
182186	Dec-04	Suicidal Tendency	Suspected	Serious
178601	Dec-04	Suicide Attempt	Concomitant	Serious
179268	Dec-04	Suicide attempt	Concomitant	Serious
183973	Mar-05	Suicidal Tendency	Suspected	Serious
154637	Mar-06	Thoughts of Self Harm	Suspected	Serious
187626	-	Suicidal Tendency	Treatment	Serious

Health Canada Adverse Drug Reaction Database - Gabapentin Psychobiologic Adverse Events

Report ID	Event Date	Adverse Event	Gabapentin Suspect Status	Serious/ Not Serious
163687	Jun-96	Depersonalization	Suspected	Serious
139540	1998	Apathy Thinking abnormal Depression aggravated	Treatment	Serious
128164	Oct-99	Agitation	Concomitant	Not Serious
128668	Dec-99	Agitation	Suspected	Not Serious
136254	Nov-00	Agitation Thinking abnormal	Concomitant	Serious
136341	Dec-00	Psychiatric disorders	Concomitant	Serious
140081	Apr-01	Condition aggravated Drug abuse Depression	Concomitant	Serious
151640	May-01	Psychosis aggravated Agitation Aggressiveness	Concomitant	Serious
141335	Jun-01	Aggressiveness Confusion Irritability Paranoid reaction	Suspected	Serious
141827	Jun-01	Psychotic state	Suspected	Serious
140785	Jul-01	Anxiety Confusion Agitation Accidental overdose	Concomitant	Serious
144351	Dec-01	Mood swings	Suspected	Not Serious
147522	Jan-02	Agitation Anxiety	Concomitant	Not Serious
146850	Feb-02	Emotional lability	Concomitant	Serious
164556	Mar-02	Confusion Agitation Paranoid reaction Somnolence Disorientation	Concomitant	Serious

Health Canada Adverse Drug Reaction Database - Gabapentin Psychobiologic Adverse Events

Report ID	Event Date	Adverse Event	Gabapentin Suspect Status	Serious/ Not Serious
163942	May-02	Irritability Cognitive disorders Concentration impaired Mood Swings	Concomitant	Serious
149090	May-02	Agitation	Concomitant	Serious
153298	Jul-02	Agitation Tics	Concomitant	Serious
169805	2002	Psychosis Depression aggravated	Concomitant	Serious
164064	Sep-03	Psychosis aggravated	Concomitant	Serious
167689	2003	Aggressive reaction Concentration Impaired	Concomitant	Serious
176069	Apr-04	Drug Withdrawal Syndrome Numbness Feeling Strange	Concomitant	Serious
171360	May-04	Agitation Personality disorder	Suspected	Not Serious
172492	Jun-04	Aggressiveness	Concomitant	Serious
176110	Jul-04	Psychosis Aggressive reaction Hallucination Personality disorder	Concomitant	Serious
176469	Sep-04	Depersonalization Thinking abnormal Anxiety Depression Emotional withdrawal Irritability	Concomitant	Serious

Health Canada Adverse Drug Reaction Database - Gabapentin Psychobiologic Adverse Events

Report ID	Event Date	Adverse Event	Gabapentin Suspect Status	Serious/ Not Serious
181285	Sep-04	Anxiety Depression Condition aggravated	Concomitant	Serious
183869	Nov-04	Agitation Apathy Anxiety Euphoria Memory loss	Concomitant	Serious
176629	2004	Aggressiveness Irritability Condition aggravated	Concomitant	Serious
182556	Feb-05	Emotional lability	Concomitant	Not Serious
188276	Apr-05	Confusion Agitation Irritability Hallucination	Concomitant	Serious
185695	May-05	Personality disorder	Suspected	Not Serious
158226	-	Thinking abnormal Paranoia aggravated Hallucination auditory	Suspected	Serious
132718	-	Panic reaction	Concomitant	Serious
178555	-	Psychotic reaction NOS	Concomitant	Serious

AMERICAN ASSOCIATION OF POISON CONTROL CENTERS

184. Data from the 1996-2002 annual reports of the Toxic Exposure Surveillance System compiled by the American Association of Poison Control Centers, which used human poison reports from almost all of the poison control centers in the US, were reviewed. The reports were published in the American Journal of Emergency Medicine and include all concomitant medications as well as the primary suspect in the overdose. From these reports, 32 instances of a poisoning death in which a patient was taking gabapentin were observed. Twenty-eight of these reports were intentional overdoses; the remaining four were for either unknown or adverse reaction reasons. Of the 28 intentional overdoses, 2 of them were in patients who were only taking gabapentin. Another patient was receiving only gabapentin and the antihypertensive agent diltiazem, a drug product not associated with suicide-related events. The table below provides an overview of these events.

Neurontin (Gabapentin) Adverse Events American Association of Poison Control Centers (Derived from American Journal of Emergency Medicine)			
Annual Report/Case Number	**Drug**	**Adverse Event**	**Blood Concentration**
1996/441	Imipramine	Intentional Suicide	Unknown
	Clonazepam		
	Gabapentin		
1997/273	Acetaminophen	Intentional Suicide	Unknown
	Propoxyphene		
	Carisoprodol		
	Gabapentin		
1998/428	Amitriptyline	Intentional Suicide	Unknown
	Acetaminophen /Hydrocodone		
	Gabapentin		
1998/444	Amitriptyline	Intentional Suicide	Unknown
	Sertraline		
	Gabapentin		
1998/498	Sertraline	Intentional Suicide	Unknown
	Zolpidem		
	Gabapentin		
1998/585	Diltiazem	Intentional Suicide	Unknown
	Gabapentin		
1998/687	Temazepam	Intentional Suicide	2330 ng/mL
	Gabapentin		
	Amitriptyline		

Neurontin (Gabapentin) Adverse Events American Association of Poison Control Centers (Derived from American Journal of Emergency Medicine)			
Annual Report/Case Number	**Drug**	**Adverse Event**	**Blood Concentration**
1998/406	Valproic Acid	(Intentional Suicide/Patient Narrative)	500 mg tablets (UNK)
	Gabapentin		300 mg tablets (UNK)
	Nefazodone		100 mg tablets (UNK)
1999/430	Opiate	Intentional Suicide	Unknown
	Gabapentin		
	Unknown Drug		
1999/458	Gabapentin	Intentional Suicide	
	Aspirin		56 mg/dL
	Activated Charcoal		
1999/523	Bupropion	Intentional Suicide	Unknown
	Olanzapine		
	Gabapentin		
1999/569	Paroxetine	Intentional Suicide	Unknown
	Gabapentin		
1999/575	Tricyclic Antidepressant	Intentional Suicide	Unknown
	Gabapentin		
	Paroxetine		
2000/293	Acetaminophen /Codeine	Intentional Suicide	Unknown
	Fosinopril		
	Gabapentin		

Neurontin (Gabapentin) Adverse Events American Association of Poison Control Centers (Derived from American Journal of Emergency Medicine)			
Annual Report/Case Number	**Drug**	**Adverse Event**	**Blood Concentration**
2000/469	Oxycodone	Intentional Suicide	Unknown
	Gabapentin		
	Paroxetine		
2000/496	**Gabapentin**	Intentional Suicide	Unknown
2000/547	Amitriptyline	Intentional Suicide	Unknown
	Gabapentin		
	Zolpidem		
2000/610	Nortriptyline	Intentional Suicide	75 mg tablets (80/Patient Narrative)
	Gabapentin		Unknown
2000/784	Haloperidol	Intentional Suicide	Unknown
	Benztropine		
	Gabapentin		
2000/800	Quetiapine	Adverse Reaction	Unknown
	Gabapentin		
	Indinavir		
2000/810	Zolpidem	Adverse Reaction	Unknown
	Gabapentin		
2001/565	**Gabapentin**	Intentional Suicide	Unknown
2001/566	Gabapentin	Unknown	Unknown
	Risperidone		
	Benztropine		

Neurontin (Gabapentin) Adverse Events American Association of Poison Control Centers (Derived from American Journal of Emergency Medicine)			
Annual Report/Case Number	**Drug**	**Adverse Event**	**Blood Concentration**
2001/567	Gabapentin	Intentional Suicide	Unknown
	Risperidone		
	Benztropine		
2001/568	Gabapentin	Intentional Suicide	Unknown
	Tramadol		
	Rofecoxib		
2001/607	Amoxapine	Intentional Suicide	Unknown
	Quetiapine		
	Gabapentin		
2001/881	Alprazolam	Unknown	148 ng/mL
	Meprobamate		Unknown
	Gabapentin		Unknown
2002/364	Acetaminophen /Hydrocodone	Intentional Suicide	Unknown
	Amitriptyline		
	Gabapentin		
2002/531	Methadone	Intentional Suicide	Unknown
	Olanzapine		
	Gabapentin		
2002/662	Amitriptyline	Intentional Suicide	Unknown
	Gabapentin		
	Hydroxyzine		
2002/707	Doxepin	Intentional Suicide	Unknown
	Gabapentin		
	Olanzapine		

Neurontin (Gabapentin) Adverse Events American Association of Poison Control Centers (Derived from American Journal of Emergency Medicine)			
Annual Report/Case Number	**Drug**	**Adverse Event**	**Blood Concentration**
2002/708	Doxepin	Intentional Suicide	Unknown
	Gabapentin		
	Sertraline		

DRUG ABUSE WARNING NETWORK (DAWN)

185. The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related visits to hospital emergency departments and drug-related deaths investigated by a medical examiner. The number of emergency department visits where gabapentin was listed have steadily increased since 1997, and by 2002 represented a significant number compared to other anticonvulsant agents (see table, below). Even though Pfizer Defendants have continuously argued that gabapentin is not a drug of abuse, the FDA noted in the December 2004 NDA approval for Lyrica® (pregabalin, a compound structurally similar to gabapentin) that based on DAWN data, gabapentin has been reported responsible for a significant number of emergency room visits associated with abuse and/or misuse. In fact, when corrected for prescription ranking, gabapentin reports represent a significant contribution to the overall DAWN data. Although these data do not provide specific information as to the nature of the event (*i.e.*, if it was related to suicidal behavior), these events, combined with the alarming signals observed in other databases (AERS, Pfizer Defendants' internal database, WHO) confirmed that patients should have been warned appropriately of the risks of gabapentin.

Drug Abuse Warning Network (DAWN) – Emergency Department Mentions for Selected Anticonvulsants
(1995-2002)

Drug name	Total 1995	Total 1996	Total 1997	Total 1998	Total 1999	Total 2000	Total 2001	Total 2002
Anticonvulsants.....	10,455	11,496	12,193	13,990	14,938	16,849	14,642	16,681
carbamazepine.....	3,633	3,743	3,473	3,221	3,113	2,276	1,827	2,029
divalproex sodium.....	2,550	4,099	5,155	6,228	5,984	6,235	5,365	5,645
felbamate.....	3	1	2	2	0	0	0	7
fosphenytoin.....	0	0	0	0	...	6	0	0
gabapentin.....	**20**	**...**	**296**	**1,002**	**2,395**	**4,465**	**3,461**	**4,465**
lamotrigine.....	0	0	...	...	...	...	323	390
oxcarbazepine.....	0	0	0	0	0	0	...	543
phenytoin.....	3,573	2,923	2,426	2,974	2,766	2,239	1,795	2,034
primidone.....	211	23	...	...	19	12	9	...
tiagabine.....	0	0	0	0	0	0	...	315
topiramate.....	0	0	0	...	...	540	621	622
valproic acid.....	449	598	618	263	357	916	...	436
anticonvulsants-NOS...	6	7	...	7	0	...	9	19

NEURONTIN RESEARCH REPORTS (1996-2002)

186. Research reports for the studies reviewed during the time period October 1996 – May 2002 contained no specific mention of positive dechallenge or rechallenge events following the occurrence of an adverse event. There were however, numerous reports of patients recovering from a psychobiologic adverse event following withdrawal from the study in which they participated. These events are listed below.

Neurontin Dechallenge Events
October 1996- December 2002
(All were withdrawals from the study)

Event (Number)	Patient/ Center #	Study #	Dose (mg/day) (mg/kg/day)	Relationship*
Thinking Abnormal (7)	Unknown	430-00124 (945-295)	1800	Possibly
	Unknown	430-00124 (945-295)	1800	Possibly
	113/003	430-00125 (945-306)	2400	Possibly
	1/6	720-03928 (945-86/186)	Unknown	Probably
	63/4	995-00085 (945-217)	Unknown	Probably
	67/4	995-00085 (945-217)	Unknown	Probably
	120/9	995-00085 (945-217)	Unknown	Possibly
Confusion (5)	Unknown	995-00070 (945-211)	Unknown	Unknown
	Unknown	430-00124 (945-295)	2400	Possibly
	114/003	430-00125 (945-306)	900	Possibly
	020/010	720-03827	4800	Unlikely
	182/6	995-00085 (945-217)	Unknown	Probably
Hostility (3)	1/6	720-03928 (945-86/186)	Unknown	Probably
	6/6	720-03928 (945-86/186)	600	Definitely
	7/29	720-03928 (945-86/186)	1200	Probably

*Relationship of the adverse event to gabapentin

Neurontin Dechallenge Events (*continued*)
October 1996- December 2002
(All were withdrawals from the study)

Event (Number)	Patient/ Center #	Study #	Dose (mg/day) (mg/kg/day)	Relationship
Agitation (2)	020/010	720-03827	4800	Unlikely
	004/019	720-03827	3600	Possibly
Hyperkinesia (2)	004002/04	720-04335 (945-301/401)	34.4	Possibly
	2/13	720-03928 (945-86/186)	600	Possibly
Emotional Lability (2)	021001/21	720-04335 (945-301/401)	37.5	Probably
	1/3	720-03928 (945-86/186)	900	Definitely
Personality Disorder (2)	6/6	720-03928 (945-86/186)	600	Definitely
	120/9	995-00085 (945-217)	Unknown	Possibly
Psychosis (2)	020/010	720-03827	4800	Unlikely
	001/005	720-03827	4800	Unlikely
Depersonalization (1)	9005/90	720-04130 (945-224)	2400	Probably
Depression (1)	011/013	430-00125 (945-306)	300	Probably
Disorientation (1)	354/036	430-00125 (945-306)	900	Probably
Nervousness (1)	028/010	720-03827	2700	Possibly

* Relationship of the adverse event to gabapentin

IV(d) ***Gabapentin Regulatory Events (1996-2002)***

187. A chronologic review of the time period at issue reveals pertinent regulatory actions and events by Pfizer Defendants and FDA regarding Gabapentin, including labeling changes and warning letters to Pfizer Defendants.

188. Gabapentin Labeling Change Related to Postmarketing Events: On or about February 13, 1997, Pfizer Defendants (Parke-Davis) submitted an NDA (Supplement 7) package detailing changes to be made to the gabapentin product label. The addition read as follows:

> **Post-introduction Reports**
> Adverse events associated with Neurontin that have been received since market introduction, that are not listed above, and that may have no causal relationship to drug, include the following: erythema multiforme, Stevens-Johnson syndrome and elevated liver function tests.

189. On or about July 16, 1997, FDA suggests the following wording for the gabapentin label:

> **Post-marketing and Other Experience**
> In addition to the adverse experiences reported during clinical testing of Neurontin, the following adverse experiences have been reported in patients receiving marketed Neurontin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, hepatotoxicity, hyperthermia, jaundice, neuroleptic malignant syndrome, pancytopenia, toxic epidermal necrolysis.

190. On or about January 5, 1998, a teleconference was held between Janeth Turner (Parke-Davis), Russel Katz and Jackie Ware (FDA). Subsequent to this call, Parke-Davis proposed the following wording:

> **Post-marketing and Other Experience**
> In addition to the adverse experiences reported during clinical testing of Neurontin, the following adverse experiences have been reported in patients receiving marketed Neurontin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: blood glucose fluctuation in diabetic patients, erythema multiforme, elevated liver function tests, fever, Stevens-Johnson syndrome.

191. On or about January 14, 1998, a teleconference was held between Russell Katz and Jackie Ware of FDA and several members of Pfizer Defendants to discuss revisions to the Post-marketing and Other Experiences section of the gabapentin package insert. Interestingly, Dr. Katz discussed FDA's criteria for addition of adverse events into a label. An internal Parke-Davis memo notes that FDA's general rule "…is to add even a single report if it is a "half way decent" report with no obvious

reason not to include it."[65] During this meeting the wording for this section was agreed upon and Parke-Davis noted that they would submit the revised insert.

192. Pfizer Defendants Underestimated Rate of Adverse Events: On or about October 1, 2001, FDA correspondence expressed concern that Pfizer Defendants (Pfizer) were underestimating the rate of adverse events observed at lower doses of gabapentin. Dr. Sharon Hertz (FDA Medical Officer) expressed concern that the presentation of adverse events for 5 pivotal controlled studies in neuropathic pain was underestimating the true occurrence of adverse events at the lower doses.[66] Adverse events were presented according to the randomized dose and not the actual dose achieved, thus making the drug appear safer since many patients did not achieve the highest randomized dose of 3600 mg.

193. Gabapentin Labeling: Reports of Hallucinations or Agitation: Internal Pfizer Defendant documents note that discussions took place as to the inclusion of the adverse event terms hallucinations and agitation in the gabapentin product labeling.[67] Safety databases were reviewed for the preferred adverse event terms "hallucinations" and agitation through March 31, 2002. Of 163 cases of hallucinations reported, 152 were excluded due to various reasons (intercurrent illness, poor documentation, concomitant medication). In the 11 remaining reports there was one positive rechallenge and 10 reports of a positive dechallenge. The document notes that the term hallucinations should be added to the gabapentin labeling. A similar search for agitation revealed 114 cases, with 106 excluded due to similar reasons. In the 8 remaining reports there were 6 positive dechallenges and 2 reports of a positive rechallenge. The memo notes that "[t]hese reports however do not provide strong substantiation of a relationship between 'agitation' and gabapentin." As these terms were already included in the adverse events observed in clinical trials section of the label, this discussion was presumably related to the inclusion of these terms in the Post-marketing section. Nevertheless, neither of these terms are present in the Post-marketing section of the current label.

194. Post herpetic Neuralgia NDA: In May of 2002, Pfizer Defendants (Pfizer) received FDA approval for gabapentin in the treatment of post herpetic neuralgia (NDA #'s 21-397; 21-423; 21-424). Pfizer Defendants originally hoped to gain approval for the more global indication of neuropathic pain but was informed by FDA that insufficient data existed for pain associated with diabetic peripheral neuropathy. Subsequent to this decision, Pfizer Defendants filed the NDA for post herpetic neuralgia and was granted approval. This marked only the second (and last) indication for which gabapentin was approved (in addition to adjunctive epilepsy therapy). Despite this, Pfizer Defendants marketed gabapentin for a wide range of off-label uses, including other types of neuropathic pain and psychiatric indications. Although Pfizer Defendants did perform clinical trials in panic disorder and bipolar disorder, either insufficient data were generated or positive results were not obtained.[68] Pfizer Defendants continued to market gabapentin for these off-label uses without seeking regulatory approval.

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[65] *See* WLC_JTurner_000230-31

[66] *See* NDA21397_MISC_008_0085-87

[67] *See* Pfizer_THo_0011190-94;

[68] *See* Pfizer_LTive_0008792-8800, entitled Gabapentin (Neurontin) CI-945 Clinical Development Plan (January 20, 1999), Section 3.3. Psychiatry Studies, at 0008800. "It is concluded that the methodology of add-on trials for [bipolar disorder] requires further refinement and the inability to control potential confounding variables is a major limitation of this design. No further trials are planned with gabapentin in any psychiatric indications."

Division of Drug Marketing, Advertising and Communications (DDMAC)
Warning Letters

195. Promotional Materials for Pediatric Indication Misleading: On or about April 19, 2001, Pfizer Defendants (Pfizer) received a response letter from FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) in which DDMAC summarized its review of Pfizer Defendants' proposed promotional materials for the pediatric indication for Neurontin Oral Solution.[69] The FDA indicated the materials were "misleading" in light of "neuropsychiatric adverse events in pediatric patients," "inconsistent with the [package insert] for Neurontin," and "lack fair balance"[70]

196. Warning Letter for Misleading Promotion: On or about July 2, 2001, Pfizer Defendants (Pfizer) received a letter from the Division of Drug Marketing, Advertising and Communications (DDMAC) recommending that they (Pfizer) discontinue the use of a slim jim containing claims of improvement in quality of life parameters in patients taking gabapentin. These claims were based on the open-label Neurontin Evaluation of Outcomes in Neurological Practice (NEON) study.[71]

[69] *See* Pfizer_LCastro_0073452.
[70] *See* Pfizer_LCastro_0073452.
[71] *See* Pfizer_LCastro_0039757-59

CONCLUSIONS (1996-2002)

197. A number of data sources were reviewed to determine the extent and severity of psychobiologic adverse events associated with Neurontin. These sources included the Pfizer Defendants PSURs, internal adverse event database, the US FDA adverse event database, WHO adverse event database and the Health Canada postmarketing database.
198. The PSUR documents revealed increasing trends in the reports of intentional overdoses, confusion, hallucinations, abnormal thoughts, depression and anxiety.
199. The five year PSUR included suicides, suicidal ideation reports, suicide attempts, suicidal thoughts, psychoses, aggression and depersonalization reports.
200. The NDA reports demonstrated signals relating to suicide events, suicide attempts and intentional overdoses.
201. Suicide-related events were also included in the IND annual reports.
202. The SRS/AERS databases included significant numbers of suicide related events, completed suicides, aggression anxiety, agitation, depersonalization and depression.
203. The Pfizer Defendants' internal database revealed suicide-related events and the attendant psychobiological events.
204. The WHO database indicated that suicide attempt was the third most frequently-reported event associated with Neurontin. In addition, there were reports of depersonalization and depression.
205. The Health Canada adverse event database reported that 4% of all events associated with Neurontin related to self-harm and suicide-related events. Other events believed to be prescursors of self-injurious behavior were also reported.
206. The American Association of Poison Control Centers and the Drug Abuse Warning Network also reported instances of intentional overdoses, abuse and misuse with Neurontin.
207. These data consistently confirmed the psychobiological and self-injurious behaviors associated with Neurontin and underscored the continued need for amplification to the professional labeling.

IV(e) Evaluation of Psychobiologic Adverse Events: June 2002 – Present

208. The following section of this report reviews the period beginning in June 2002 (immediately following approval of gabapentin for treatment of post herpetic neuralgia) and continues to the present. An overview of psychobiologic adverse events associated with gabapentin and reported to postmarketing databases, including those related to suicidal behavior, is provided. A number of important gabapentin-related regulatory submissions and internal Pfizer Defendant documents relating to the issue of suicidality are addressed. These events provide additional support to evidence provided in previous sections of this report demonstrating that gabapentin is associated with serious, often life-threatening events and underscore the unmet need for enhanced labeling regarding the potential psychobiologic adverse events, including suicide.

209. A discussion of Pfizer's 2004 (September, November) submissions to the FDA responding to the Agency's request for information relating to completed suicides or suicide attempts in patients receiving gabapentin is provided below. The response documents provided overviews of completed suicides and attempted suicides occurring during gabapentin clinical trials and those reported to the Pfizer Defendants' internal postmarketing database. A document entitled "Gabapentin and Suicide", authored by Pfizer Defendants Director of Safety Analysis (Tina Ho) which reviews suicide events reported to Pfizer Defendants' internal postmarketing database, including those occurring during clinical studies, is also reviewed. Events occurring prior to the September 2004 FDA submission are also noted, including internal Pfizer Defendants' correspondence noting the incidence of suicide-related data in the Pfizer Defendants' internal database and medical literature and FDA correspondence relating to the submissions.

210. In March of 2005 an additional FDA request was presented to Pfizer Defendants asking for information concerning suicide-related adverse events occurring during gabapentin clinical trials. This request came soon after FDA required a number of pharmaceutical companies manufacturing antidepressants (including Pfizer) to update their product label to include a black-box warning that these agents could increase the risk of suicidal thoughts and behavior in children and adolescents. Although Pfizer Defendants responded to this request in September 2005, a copy of this response has not been made available.

211. Regulatory interactions relating to gabapentin are also discussed, including Pfizer Defendants' plan to seek over-the counter approval of gabapentin for use as a sleep enhancer. In addition, the change in the gabapentin product label (May 2006) to include the terms suicide and suicide attempt in the clinical trials Adverse Events section is discussed. This change occurred subsequent to FDA requests (in 2004 and 2005) to identify suicide events in clinical trials. However, this change does not reflect the numerous postmarketing reports of suicide events in patients not participating in a clinical trial. Thus, Pfizer Defendants updated the Neurontin product label using information it had at its disposal either at, or soon after, product launch in early 1994. The fact that Pfizer Defendants have not updated the Neurontin label to reflect the occurrence of these events in non-clinical trial populations demonstrates that they have not provided patients with full disclosure of the risks and benefits of Neurontin.

212. Psychobiologic adverse events contained in Pfizer Defendants' internal database are also reviewed. As evidenced in earlier sections of this report, Pfizer Defendants were aware of a number of particularly concerning adverse events related to psychobiologic function. These include significant numbers of events related to suicidal behavior. A Periodic Safety Update report from 2003-2004, referenced below, also contains numerous reports of similar events, providing additional evidence that these events continued to occur and were noted by Pfizer. Given the susceptible

populations to which gabapentin continued to be prescribed, it was imperative at this time that Pfizer Defendants update their product label to more adequately warn patients and prescribers of the risks associated with gabapentin use.

213. As in previous sections of this report, a review of adverse psychobiologic events contained in additional Postmarketing databases (Adverse Event Reporting System, AERS; World Health Organization, WHO) is also provided. These serious suicide-related events were known to Pfizer Defendants, as evidenced by internal correspondence, and should have prompted Pfizer Defendants to update the gabapentin product label to include a stronger warning related to suicide events. This need for this enhanced warning becomes apparent when one considers the near exclusive use of gabapentin by patients considered to possess an increased risk of suicidal behaviors (*i.e.*, bipolar, chronic pain, epilepsy).

214. The documents reviewed herein demonstrate that Pfizer Defendants possessed the knowledge and the capability to strengthen the gabapentin product label prior to May 2006. This strengthened wording should have included additions to both the clinical trial adverse event section (as was performed in May 2006) as well as the postmarketing section (which has yet to be performed, despite the report of numerous cases of postmarketing suicide). Sufficient numbers of suicides and suicide attempts had occurred to warrant strengthening the Neurontin label. Pfizer Defendants' delay in incorporating an enhanced warning related to suicide events represents a failure to provide adequate risk-benefit information to patients. This is especially concerning given the number of at-risk populations (with elevated rates of suicidal behavior) utilizing gabapentin (*i.e.*, Pfizer_JSu_0027004). Had Pfizer Defendants performed a more thorough examination of these events at the time of their occurrence (and prior to being asked by FDA) the need for an enhanced label warning relating to these events may have been realized earlier. Unfortunately, it was not until Pfizer Defendants were asked by FDA to examine suicide-related events occurring during clinical trials or reported to the internal postmarketing database that a minimal corrective action was undertaken in the labeling. This change does not reflect the extent of the suicide issue associated with gabapentin, a situation which ignores the right of patients to fully understand all the risks associated with gabapentin.

215. In October 2003 Pfizer Defendants became aware of an advertisement placed by a law firm noting the occurrence of suicide in patients taking gabapentin.[72] Their intention was to "…*document the exact situation* …" and prepare communications to address the advertisement. This included a review of the literature, an overview of inquiries from healthcare providers, and the number and description of suicide-related cases. While most (if not all) of this information was gathered, as described below, it is unclear if a final report was ever prepared.

216. In one email, Pfizer Defendants noted six references mentioning either suicide attempt with gabapentin (alone or in combination with other drugs) or feeling suicidal after ingestion of an overdose.

1. 1996 Fernandez MC, Walter FG, Kloster JC et al **Hemodialysis and hemoperfusion for treatment of valproic acid and gabapentin poisoning**, *Vet Hum Toxicol*, 38: 438-443.

2. 1996 Fernandez MC, Walter FG, Petersen LR et al **Gabapentin, valproic acid, and ethanol intoxication: elevated blood levels with mild clinical effects**, *J Toxicol Clin Toxicol*, 34: 437-439.

3. 2001 Matthews SC and Dimsdale JE **Priapism after a suicide attempt by ingestion of olanzapine and gabapentin**, *Psychosomatics*, 42: 280-281.

4. 2002 Paopairochanakorn, C., White, S., and Malafa, M. J.**Cardiac and Neurologic Toxicity from Lamotrigine Ingestion**, *J Toxicol Clin Toxicol*, 40: 620-621.

5. 2002 Spiller HA, Dunaway MD, and Cutino L **Massive gabapentin and presumptive quetiapine overdose**, *Vet Hum Toxicol*, 44: 243-244.

6. 2003 Klein-Schwartz W, Shepherd JG, Gorman S et al **Characterization of gabapentin overdose using a poison center case series**, *J Toxicol Clin Toxicol*, 41: 11-15.

217. In addition, they noted approximately 35 customer (consumers, physicians, pharmacists, nurses, other healthcare providers and a sales representative) calls in 2003 inquiring about the advertisement by a law firm on suicidal events associated with gabapentin. In what appears to be a draft document providing an overview of all of this information[73], Pfizer Defendants reference a medical literature document (Klein-Schwartz et al., 2003) which notes 11 cases of suicide attempt. Despite this, Pfizer's position was that they did not "… *have any recommendations regarding the management of suicidal thoughts in patients receiving gabapentin*." In addition, Pfizer Defendants note that they "…*have received spontaneous reports of suicide or suicide thoughts since the market introduction of Neurontin.*"[74] They state that they cannot use these reports to calculate incidence or estimates of drug risk because "*the number of reports received may not be reflective of the actual number of cases that have occurred*"; "*the actual number of patients receiving gabapentin at any time point is not known*" and "*a causal relationship between gabapentin and these cases has not been established.*"[75] These often-used excuses are a common tactic used to support a lack of action regarding appropriate risk/benefit communication to healthcare providers and patients.

[72] Pfizer_THO_0004952-6 at 0004953
[73] Pfizer_JSu_0026537-42
[74] Pfizer_JSu_0026537-42.
[75] Pfizer_JSu_0026537-42.

218. Furthermore, although Pfizer Defendants are correct to say that the number of reports received may not truly reflect the actual numbers of cases which have occurred, they neglect to mention that this is likely an underestimate of the true number of events, given the well-known effects of under-reporting. The actual numbers of patients receiving gabapentin seems to be somewhat of an irrelevant point. Pfizer Defendants surely understood that the profits generated by gabapentin sales were fueled predominantly by use in off-label conditions (psychiatric use, chronic pain not associated with post herpetic neuralgia). As discussed, these patients should be considered more susceptible to the serious psychobiologic events associated with gabapentin and thus should be warned adequately.

219. A *causal* relationship is not required to enhance a product label.[76] It is not necessary for Pfizer Defendants to resolve the biochemical pathway by which Neurontin leads to self-injurious behavior. After all, Pfizer Defendants claim not to know the mechanism by which gabapentin produces an antiepileptic effect or how it alleviates pain associated with post herpetic neuralgia. Despite this, Neurontin is still used for these (as well as numerous other) conditions.[77] As there is no proven mechanism demonstrating the specific *cause* for the beneficial effects, it follows that the specific *cause* of serious, potentially life-threatening events need not be demonstrated in order to warn patients.

220. In April 2004, a teleconference was held between FDA and Pfizer Defendants to discuss reports of suicide in patients taking gabapentin.[78] This may have been the result of Dr. Robert Katz (FDA) becoming aware of suicide reports in patients taking gabapentin. In fact, Dr. Robert Katz, in an interview over the impetus for FDA's inquiry, explained that it was in response, not only to the information about gabapentin, but in conjunction with having received notice from another pharmaceutical company that was developing an anticonvulsant:

> [I]t came about because a company came to us after looking at their controlled trial database. They thought they might have seen a signal of increased suicidal behavior in their clinical trials….[H]e could not name the drug at this time. But, he said, there is another anticonvulsant drug that has already been linked with a slight increase in suicide risk. Zonisamide has on its label a rate of 1.1 percent suicide attempts versus 0.4 percent for placebo, Dr. Katz said. So, taken together with this second drug, whose sponsor felt might have a signal, we suggested that we might look back at all the newer anticonvulsants.[79]

221. The April 2004 conference was apparently the first in a series of meetings held between FDA and Pfizer Defendants to discuss the submission of a report on suicides and suicide attempts occurring in patients receiving gabapentin. Soon after this (May 2004), a Citizen's Petition was submitted by Finkelstein & Partners, requesting an amplification of the gabapentin labeling to reflect

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[76] 21 CFR 201.57 (2007) provides that a product's "labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established".

[77] According to Pfizer Defendants' employee, John LaMattina, they 4"really DO know the mechanism with a relatively high degree of confidence." Pfizer_CTaylor_0017230. Further, in discussing mechanism of action of Neurontin in terms of its GABA neurotransmitter activity in the human brain, Pfizer Defendants' employee Douglas Feltner indicated the reality of the increases in GABA in human brain, and stated, " I suppose the question is: what are the consequences of the increases in GABA in human brain that are caused by gabapentin? It strikes me that they might contribute to efficacy and adverse events in humans." Pfizer_CTaylor_0015442.

[78] Pfizer_LCastro_0026268.

[79] *See* Neurology Today, Volume (5)6, June 2005, pp. 1, 12-14. *See* Depo. Manfred Hauben, 7/13/07, at Ex.7.

the "*significant number of postmarketing reports of completed suicides, suicidal attempts and suicidal ideations*."[80] This petition was based upon postmarketing events of completed suicide and suicide-related events associated with gabapentin and reported to FDA's Adverse Event Reporting System. There were 8 completed suicides from 1998 through 2002 and 17 suicides recorded between January and June 2003. This petition asked that appropriate measures be taken to warn patients and prescribers of these suicide-related risks. This included the addition of strengthened wording in the product label and the dissemination of a Dear Healthcare provider letter providing physicians and prescribers with information relating to the screening and monitoring of patients receiving gabapentin.

222. In August 2004, Tina Ho, Director of Safety Analysis for Pfizer, authored a document entitled "Gabapentin and Suicide".[81] This document reviewed postmarketing reports of suicide and suicide attempt observed in subjects receiving gabapentin. The Tina Ho document reviewed only postmarketing suicide-related events (including clinical study cases) reported to Pfizer Defendants' internal postmarketing database. In clinical study and "solicited cases" she noted the occurrence of 3 cases of completed suicide and 7 cases of suicide attempt. These 3 cases of completed suicide (all male patients) are distinct from the 2 cases (both female) of completed suicide reported to FDA in September 2004.[82] Pfizer Defendants did describe 3 cases of completed suicide in the FDA submission under Postmarketing Data, clinical study cases. These cases may represent the same clinical study patients noted by Ho; however, this could not be determined conclusively, as Pfizer Defendants did not provide information about these patients in their September 2004 FDA submission.

223. Non-clinical study cases of completed suicide (35) and suicide attempt (73) provided by the Ho document and the FDA submission are identical. These 35 cases of suicide represented 0.2% of the total number of gabapentin postmarketing cases reported to the database. Twenty-two of these cases originated from the literature (American Association of Poison Control Centers). Pfizer Defendants concluded that the Postmarketing data on suicide and suicide attempts "… *do[es] not support a causal association between gabapentin and suicide or suicide attempt*".[83] Despite this, an early draft of the Tina Ho document included the following erroneous statement which was later removed "*A review of the available postmarketing data on gabapentin cases reporting suicide or suicide attempt reaffirms the inclusion of suicide as one of the adverse events observed during gabapentin therapy*…."[84]

224. Of note, patient histories for those patients completing a suicide attempt are included in the Tina Ho document, apparently in an attempt to mitigate the role of gabapentin in the completed suicide. As such, one patient had a history of depression and "*social problems*", and another patient "…*committed suicide most likely due to social reasons* …."[85] One case of suicide attempt may have been considered related to gabapentin but it is unclear whether the causality assessment referred to the suicide attempt or to another adverse event (somnolence).[86] This serves as another example of a possible dilution of serious psychobiological adverse events.

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[80] *See* Deposition of Lloyd Knapp (June 28, 2007) at Exhibit 40 for Citizen's Petition, dated May 17, 2004. In part, the Petition requested FDA to require labeling additions to the Neurontin package insert the Precautions section, Adverse Reactions section, as well as the addition of a Bolded Black Box Warning.

[81] *See* Pfizer_THO_0005262-73

[82] *See* Response to FDA Regarding Suicide and Suicide Attempts in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance, September 2004

[83] *See* Pfizer_THO_0005262-73 at 0005263

[84] *See* Pfizer_THO_0005335– 95 at 0005389

[85] *See* Pfizer_THO_0005262-73 at 0005265

[86] *See* Pfizer_THO_0005262 at 0005265. This patient was exposed to Neurontin during an open-label Painful Diabetic Neuropathy Study and experienced adverse events including suicide attempt, intentional overdose and somnolence. Pfizer

PFIZER RESPONSE TO FDA INQUIRY REGARDING SUICIDE AND SUICIDE ATTEMPT
(*September 2004; November 2004****)***

225. Pfizer's 2004 submission to the FDA regarding instances of suicide and suicide attempt observed during clinical trials occurred in two parts: in September 2004, Pfizer Defendants provided their review of completed suicides, attempted suicides and deaths occurring during 92 Phase II-IV gabapentin studies (>9000 patients), including placebo- and non-placebo-controlled studies as well as open-label studies, in various patient populations (epilepsy, various pain disorders, psychiatric disorders).[87] The second submission (November 2004) encompassed Pfizer's review of Phase I gabapentin studies (55 studies).[88] There were no cases of suicide or suicide attempt in Phase I gabapentin trials.

226. From the 92 clinical studies analyzed (September 2004 Submission), Pfizer Defendants identified 2 cases of completed suicide and 12 cases of suicide attempt. Both cases of suicide occurred in patients taking the drug for epilepsy and both were considered not related to gabapentin One of the suicide cases occurred in a non-placebo-controlled study and the other occurred 6 months after the patients participation in a trial had ended (this patient also *attempted* suicide while participating in the trial). There were no cases of completed suicide in patients receiving placebo. The majority of the suicide attempt cases noted in the September 2004 submission (11/12) were epileptic patients; one patient participating in a neuropathic pain study attempted suicide. Of these 12 suicide attempts, 11 occurred in uncontrolled trials (one occurred in a placebo-controlled trial). Nine of the 12 were considered unrelated to gabapentin treatment (3 were considered related to gabapentin). There were no cases of suicide attempt in placebo treated patients.

227. Importantly, during an open-label Painful Diabetic Neuropathy Study, a patient exposed to Neurontin experienced adverse events including suicide attempt, intentional overdose and somnolence. Pfizer Defendants' causality assessment as summarized in an ISS of Safety in 2001 demonstrated the suicide attempt and intentional overdose were definitely related to Neurontin.[89] Later, in a 4-Month Safety Update, these definitely related causality assessments were again confirmed.[90] However, these causality assessments are subsequently removed as to suicide attempt and intentional overdose, and only somnolence remained as the adverse event with a definite relationship to Neurontin. Details surrounding the "follow-up information" that Pfizer Defendants indicated to FDA in the September 2004 resulted in the removal of said causality assessments.[91]

228. The September submission also included a reference to Psychiatry Studies and indicated there were no suicides or suicide attempts reported in any of the studies conducted for the psychiatric disorders (bipolar disorder, panic disorder, and social phobia).[92] However, the demographics and small exposure data from the psychiatry studies, as summarized in the September 2004 submission, demonstrate the likelihood of observing such rare events was not going to happen anyway; there were only 144 total patients exposed to gabapentin over the span of all three (3) studies (bipolar

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Defendants' causality assessment as summarized in an ISS of Safety in 2001 demonstrated the suicide attempt and intentional overdose were definitely related to Neurontin. *See* RR-REG 720-30077 (ISS of Safety for Gabapentin for Neuropathic Pain, issued July 9, 2001, at p.362).

[87] Pfizer_MPatel_0039110.

[88] Pfizer_LCastro_0068931-945.

[89] *See* RR-REG 720-30077 (ISS of Safety for Gabapentin for Neuropathic Pain, issued July 9, 2001, at p.362).

[90] *See* RR-REG 720-30134 (4 Month Safety Update for Gabapentin for Neuropathic Pain, issued November 28, 2001, at p.59).

[91] *See* Pfizer_MPatel_0039110 at 0039165.

[92] *See* Pfizer_MPatel_0039110 at 0039136.

disorder, panic disorder, social phobia).[93] Consequently, it is of little persuasive value that there were no suicides or suicide attempts in such a small population exposed to Neurontin.

229. The September submission also included postmarketing cases of suicide or suicide attempt reported to Pfizer's internal database. The postmarketing (internal) database reviewed in the September 2004 submission included spontaneous reports, reports from health authorities, medical literature reports, events from clinical studies and events from Pfizer-sponsored marketing programs. Pfizer Defendants noted that suicide clinical study cases contained in the postmarketing database "…*may or may not have been captured in the review of clinical trial data presented earlier*…".[94] Included data was current through March 31, 2004 and obtained from an estimated 12 million patients worldwide. Out of a total of 17,768 submitted adverse events, Pfizer Defendants noted 35 cases of completed suicide and 73 suicide attempts. As Appendix D was deleted from this submission, additional information related to the postmarketing suicide-related events was not reviewed.

230. The Postmarketing review provided by Pfizer Defendants detailed completed suicides and suicide attempts occurring in two separate patient populations – non-clinical study cases and clinical study and solicited cases. A total of 35 non-clinical study cases of completed suicide were reported to the Postmarketing database. Limited data for causality assessment were provided for the majority of these reports (25/35). The remaining 10 cases of completed suicide were noted to have contributing or confounding factors according to Pfizer. These included "… *pre-existing psychiatric conditions, severe chronic pain, other recent events, and an unlikely temporal association with gabapentin therapy*."[95] Twenty-two of the 35 completed suicide cases originated from the literature (based on data from the American Association of Poison Control Centers, 1996-2004). In one case, the suicide was considered "linked" to gabapentin.[96]

231. The internal Pfizer Defendant Postmarketing database contained 73 non-clinical cases of suicide attempt. The majority of the reports in both the FDA submission were noted as having contributory or confounding factors. The September 2004 FDA submission reported 3 cases of suicide attempt in which the temporal association was unlikely or unknown and 3 cases in which the patient exhibited no previous risk factors. Two of these 3 cases developed depression prior to the suicide attempt and a positive dechallenge was noted in one of these patients (001-0945-980441, a 27 year old male). This patient was also restarted on gabapentin with no recurrence of his symptoms (negative rechallenge).

232. The September 2004 FDA submission and the Tina Ho document (*e.g.*, "Gabapentin and Suicide") discuss the occurrence of completed suicide events and attempted suicides in patients taking gabapentin. The September 2004 submission reported events occurring during clinical studies as well as postmarketing reports while the Tina Ho document reported only those events contained in the Pfizer Defendants' internal database.

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[93] *See* Dep. of Pfizer Defendants' witness, Manfred Hauben (Medical Dir. of Risk Management Strategy) (July 12, 2007) at p.194-195. "Q. Do you agree or disagree that premarketing trials are rarely large enough to detect small differences in the risk of common adverse events or to reliably estimate the risk of rare events? . . . A. Generally, clinical trials are not – are not powered to detect --- rare events . . . ." *See* Dep. of Pfizer Defendants' witness, Manfred Hauben (Medical Dir. of Risk Management Strategy) (July 12, 2007) at p.253. "Q. Are you familiar with the theory called the Rule of 3s? A. Yes. Q. Can you explain it to us? A. Yes. If you have something with an incidence of, say, one in a thousand, to be 95 % confident of observing one or more cases, you would want to -- you'd have a series of 3000 people."

[94] *See* Response to FDA Regarding Suicide and Suicide Attempts in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance

[95] *See* Response to FDA Regarding Suicide and Suicide Attempts in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance

[96] *See* Response to FDA Regarding Suicide and Suicide Attempts in Neurontin® (gabapentin) Clinical Trials and Postmarketing Surveillance

233. It is likely that some of the suicide attempts reported to FDA in the September 2004 submission are the basis for inclusion of the terms "suicidal" and "suicide gesture" in the product label under Adverse Events Observed in Clinical Trials. However, the far greater numbers of postmarketing suicide and suicide attempt reports, coupled with the almost exclusive off-label use of gabapentin, demonstrates the need for additional language warning all patients (not just epileptics and patients with pain associated with post herpetic neuralgia). Despite this, no mention is made of suicide or suicidal behavior in the gabapentin product label under the postmarketing section. Pfizer Defendants should have recognized the steadily increasing numbers of these postmarketing suicide-related events and incorporated meaningful labeling changes to reflect the suicide-related risks associated with gabapentin use. The recent minor change to the gabapentin label (incorporating the terms suicide and attempted suicide) was enacted far too late, does not adequately convey the extent and seriousness of these events and occurred only following a regulatory inquiry into these suicidal events.

MARCH 2005 FDA RESPONSE FOR SUICIDE-RELATED ADVERSE EVENTS OCCURRING DURING GABAPENTIN CONTROLLED CLINICAL TRIALS

234. In March of 2005, FDA requested that Pfizer Defendants identify all trials in the gabapentin development program meeting the following criteria: placebo-controlled; parallel arm; short term (up to 6 months); at least 30 patients' total.[97] Following this, FDA provided Pfizer Defendants (and other pharmaceutical manufacturers) a search strategy to identify and further evaluate "*possibly suicide related*" adverse events occurring in these trials.[98] Events were required to have happened within 1 day of stopping randomized treatment. The classification of "*possibly suicide-related*" adverse events was based on an approach used for identification of these events in pediatric patients taking SSRIs (see September 13-14, 2004, FDA Advisory Committee Meeting). Following numerous correspondences between FDA and Pfizer Defendants over the criteria used to determine "possibly suicide related" adverse evetns, criteria arguably too narrow to appropriately reflect all psychobiologic adverse events including suicidal events, Pfizer Defendants provided their response with accompanying data on June 22, 2006. Applying the data in a form and fashion consistent with the limited protocol, Pfizer Defendants maintained their position to FDA that Neurontin was not associated with an increased risk of suicidal behavior.[99]

235. As Pfizer's submission was limited to only serious psychiatric adverse events occurring in short-term, placebo controlled trials, Pfizer Defendants were not required to report other important psychiatric adverse events.[100] For example, the following serious adverse events which occurred in

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[97] *See* Letter from Russell Katz, MD (FDA) to Manini Patel, Pfizer; March 16, 2005

[98] *See* Letter from Russell Katz, MD (FDA) to Manini Patel, Pfizer; March 16, 2005; Carroll, 2005 FDA Reviews Data on Anticonvulsants for Suicide Risk

[99] *See* Pfizer_MEvertsz_0079431.

[100] Importantly, Pfizer Defendants' submissions to FDA did not qualify as pharmacoepidemiological studies; the clinical trials upon which Pfizer Defendants' provided their submission could best be deemed only a 'case series' evaluation. Moreover, the clinical trials were not designed to detect rare events of a psychiatric nature, particularly suicidal behavior. *See* deposition of Manfred Hauben (Medical Dir. Risk Management at Pfizer), July 12, 2007 at pp 230-234: Q. You are aware that the company, Pfizer, has provided certain evaluations to the FDA in 2004 and 2005, and possibly in 2006, in response to an inquiry by the FDA about suicidaility, right? A. Yes. Q. Was that considered a pharmacoepidemiologic study by Pfizer? A. I don't think the reports were titled that . . . . Q. Notwithstanding what the title was of any of the documents submitted, do you consider the substance of the documents to be pharmacoepidemiologic studies? A. These reports were not case-control studies and they were not cohort studies…. Q. Were they in any other way substantively to be considered pharmacoepidemiologic studies? A. I would not describe them as pharmacoepidemiologic studies…. Q. They were considered a case series, right? A. Well, no…. They looked at clinical trial data and spontaneous reporting data…. Q. . .

clinical trial 945-183 would not be included simply because the trial protocol did not have a placebo arm:

EVENT 1: Adverse Event: **Suicide**

Patient No. 70163, a 46-year-old Caucasian female, committed suicide while receiving 1800 mg/day of Neurontin. This event occurred on study day 15.

EVENT 2: Adverse Event: **Suicide Attempt by Drug Overdose**

Patient No. 17012, a 29-year-old Caucasian male attempted suicide by overdosing on divalproex sodium (Depakote) and Neurontin while receiving 900 mg/day of Neurontin. The event began on study day 14. The Pfizer investigator considered the event to be definitely related to Neurontin. The event was considered serious because the patient was hospitalized. Neurontin was interrupted due to this event.

EVENT 3: Adverse Event **Psychosis Leading to Self Inflicted Chest Wound**

Patient No. 29324, a 29-year-old Hispanic female, experienced a period of psychosis and a self-inflicted stab wound to the chest while receiving 2700 mg/day of Neurontin. The psychotic episode began on study day 73 and the self-inflicted stab wound to the chest occurred on study day 76. Both events were considered to be severe in intensity with the psychosis lasting for 9 days and treatment for the stab wound for 21 days.

EVENT 4: Adverse Event: **Psychosis with Suicidal Ideation**

Patient No. 23812, a 52-year-old Hispanic female, experienced an episode of psychosis while receiving 1500 mg/day of Neurontin. The event began on study day 68. The patient presented for psychiatric admission to the Emergency Room. She was hearing voices telling her to kill herself and she feared for her life.

.[T]hey were case series? A. Large case series, yeah." *See* deposition of Manfred Hauben (Medical Dir. Risk Management at Pfizer), July 12, 2007 at pp 195-196: Q. Would you agree that identification and quantification of potentially infrequent but serious risks require larger studies that are designed to distinguish between the role of background risk factors and the effects of a particular drug on the rate of outcomes? A. As a general practice, rare adverse events would require more people to detect with a given level of confidence the rare event relative to a common event. Q. And would you agree that the population being treated in the clinical trials also needs to be considered? A. For what? Q. Well, in determining --- in determining --- I should say to detect differences in the risk of common adverse events or to reliably estimate the risk of rare events? A. I don't think --- I don't think you can use clinical trials to reliably detect that.

236. The following events comprise an overview of pertinent regulatory events occurring during the period under review in this section of the report (June 2002 – August 2006). Please note that this is not an all-inclusive list of regulatory events during the current period and does not include events already covered in earlier sections of this document. During this period, Pfizer Defendants also received marketing approval for Lyrica (pregabalin), a product similar to gabapentin. Interestingly, the Lyrica product label included the terms suicide and suicide attempt at product launch, reflecting the occurrence of 1 and 3 events for each respective term.

237. Over-The-Counter Indication – Sleep Quality 2000-2003. Pfizer Defendants have pursued an over-the-counter (OTC) indication for gabapentin in the enhancement of sleep quality during the current period under study in this section.[101]. In July 2000, Pfizer Defendants submitted an IND (60,622) for this indication and have met with FDA (October 2000, January 2003) to discuss clinical protocols and review information. FDA has never been opposed to Pfizer Defendants pursuing an OTC indication, but has indicated that this is a unique situation as there is no large existing prescription database for gabapentin in this indication.[102] FDA has informed Pfizer Defendants that safety is an issue for OTC products and that adverse events listed in the gabapentin label would need to be evaluated carefully. Pfizer Defendants had hoped to use safety data obtained in epileptic patients as support for the OTC indication. However, FDA noted that additional data in the indicated population would be required and felt that the biggest question was related to safety. Indeed, FDA recognized serious adverse event reports in the epilepsy population that caused concern (it was not stated what these events were) and they were not convinced the product was "OTC-able". FDA also stated that the risks needed to be weighed against the minimal benefits to be gained.[103]

238. United States Food and Drug Administration (August 12, 2002). On June 14, 2002, Pfizer Defendants requested FDA (Division of Drug Marketing, Advertising and Communications, DDMAC) comments on gabapentin promotional materials.[104] The response by DDMAC included general comments that the promotional items overstated the efficacy of gabapentin, minimized risk information, included misleading dosage information, implied superiority claims not supported by substantial evidence, described a misleading mechanism of action, and included misleading information about the marketing experience of gabapentin.[105]

239. Potential for Drug Abuse with Gabapentin: A Post-Marketing Safety Analysis (August 16, 2002). This internal Pfizer Defendant document reviews events of drug dependence, addiction, and euphoria reported to the Pfizer Defendants' (internal) postmarketing database through a cutoff date of June 20, 2001.[106] Sixty cases were identified and evaluated (36 euphoria, 24 drug dependence or addiction), representing 0.6% of all cases entered during the same time interval. Sixteen of the 24 drug dependence or addiction cases were excluded for various reasons. Of the 8 non-excluded cases, 5 were listed as drug-abuse/addiction; 2 were listed as drug seeking behavior; and 1 described gabapentin use to relieve cocaine withdrawal effects. All 8 cases were classified as serious and 2 patients required hospitalization. Thirty-six cases of euphoria were noted. In the majority of cases, euphoria was accompanied by additional unspecified neuropsychiatric effects. Of note, euphoria

[101] *See* IND60622_MISC_002_0011-24
[102] *See* IND60622_MISC_002_0011-24
[103] *See* IND60622_MISC_002_0011-24
[104] *See* Pfizer_LCastro_0073128-32
[105] *See* Pfizer_LCastro_0073128-32
[106] *See* Pfizer_LCastro_0065672

was often reported to occur shortly after commencing gabapentin (immediately or almost immediately in 3 cases).

240. Approval of Pregabalin (Lyrica) (December 30, 2004). Lyrica was approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (see attached letter). In the initial product label, Pfizer Defendants included the terms suicide and suicide attempt to reflect, respectively, a single completed suicide and three suicide attempts. This is in contrast to the initial gabapentin label which included only the terms "suicide gesture" and "suicidal" despite receiving reports of completed suicide and suicide attempt prior to approval in December 1993. Had Pfizer Defendants (Parke-Davis) chosen to provide a more complete label for gabapentin either at or soon after product launch, the more susceptible patient populations and their prescribers would have known of these serious risks. Unfortunately, the recent label changes incorporated by Pfizer Defendants to the gabapentin label occurred only following initiation by the FDA and do not adequately convey the extent of suicide-related behavior occurring in patients receiving the drug outside of a clinical study.

241. Zoloft DDMAC Letter (May 6, 2005). Pfizer Defendants received a DDMAC letter concerning the omission of "*important information relating to the risk of suicidality in patients taking Zoloft*" from a print advertisement.[107] FDA noted that this omission was particularly concerning as "*it fails to include a serious risk associated with the drug*" and that it "*fails to reveal material facts with respect to consequences that may result from use of Zoloft.*" Thus, Pfizer Defendants once again demonstrated an unwillingness to share all risk/benefit information with patients and prescribers. Similar to the situation observed with gabapentin, patients taking Zoloft are at increased risk for drug-induced adverse psychobiologic events, a situation which requires that all risk information be adequately conveyed.

242. Gabapentin Label Change (Inclusion of "suicide" and "suicide attempt") (May 2006). Following an FDA request to identify completed suicides and suicide-related events in gabapentin clinical trials and their internal adverse event database, Pfizer Defendants received approval for their "Changes Being Effected" supplemental new drug applications in May 2006[108]. The applications were submitted on December 21, 2005, and provided for the inclusion of the terms "suicide" and "suicide attempt" in the Adverse Reactions section of the label.[109] Despite numerous postmarketing suicide-related events reported to their internal database as well as the US AERS database, Pfizer Defendants chose not to amend the postmarketing section of the label.

[107] Letter from Kay Chitale (DDMAC) to Mojgan Moghadassi (Pfizer); May 6, 2005

[108] Letter from Russell Katz, MD (FDA) to Mary Ann Evertsz (Pfizer); May 3, 2006

[109] Such language should have been added to the post-marketing safety section of the package insert as well, and this was a feasible option for Defendants. *See* Deposition of Manfred Hauben (Med. Director of Risk Management Strategy for Pfizer), July 12, 2007, pp 160-161, where in response to inquiry regarding whether to recommend implementing a Dear Doctor or Dear Healthcare Professional letter if information during post-marketing safety surveillance demonstrated changes to the risk-benefit profile of a drug, witness Hauben explained, in part, "there are various instruments or mechanisms or, you know, procedures that you do, depending on the scenario. And of course, that could range from adding an event to the adverse event section of the label. It could, in some instances, it's rather rare, sending out a Dear Doctor letter, or something in between. . . ."

PFIZER DEFENDANTS INTERNAL ADVERSE EVENT DATABASE

243. The internal adverse event database compiled by Pfizer Defendants to monitor adverse events reported to the company through various sources was reviewed. The table below provides an overview of suicide-related events and intentional overdoses reported to the Pfizer Defendants internal database between 2002 and 2005. Of note, the numbers of cases of completed suicide and suicide attempt provided in the table below are consistent with numbers reported (through March 31, 2004) by Pfizer Defendants in their September 2004 submission to FDA. As such, at the end of 2003 there were 33 cases of suicide reported to the database; Pfizer Defendants reported 35 through March 31, 2004. Similarly, there were 62 cases of suicide attempt through the end of 2003 and Pfizer Defendants reported 73 cases as of March 31, 2004.

244. Pfizer Defendants should have recognized the growing numbers of suicide attempts and completed suicides that continued to accumulate in their internal database. Between 2002 and 2003 reports of both events more than doubled, a finding which should have prompted a thorough review of these events and resulted in the necessary changes to the product label reflecting the suicidal behaviors. A similar trend was observed for both events during 2003-2004; unfortunately it was not until FDA requested an analysis of all of the suicide-related events that Pfizer Defendants undertook a complete analysis of these events.

245. Pfizer Defendants attempted to minimize these numbers by noting the elevated rates of suicide in a number of different patient populations treated with gabapentin (epilepsy, bipolar, neuropathic pain, etc.). They also noted that these numbers represented a small percentage of the total adverse events reported to the adverse event database. However, these rationalizations have been previously criticized by FDA as inadequate and not applicable for suicide-related events.[110]

[110] Alert for Healthcare Professionals: Isotretinoin (marked as Accutane), FDA; November 2005

Pfizer Defendants' Internal Database – Suicide-Related Terms (2002-2005)

Completed Suicide

Quarter	Reports	Cumulative	Cumulative Reports	Pct Total
2002 Q4	9	14	3604	0.39%
2003 Q4	1	33	4779	0.69%
2004 Q4	13	68	6269	1.08%
2005 Q4	0	76	6419	1.18%

Suicide Attempt

Quarter	Reports	Cumulative	Cumulative Reports	Pct Total
2002 Q4	1	29	3604	0.80%
2003 Q4	15	62	4779	1.30%
2004 Q4	16	118	6269	1.88%
2005 Q4	0	127	6419	1.98%

Suicidal Ideation

Quarter	Reports	Cumulative	Cumulative Reports	Pct Total
2002 Q4	4	29	3604	0.80%
2003 Q4	20	56	4779	1.17%
2004 Q4	16	117	6269	1.87%
2005 Q4	0	128	6419	1.99%

Intentional Overdose

Quarter	Reports	Cumulative	Cumulative Reports	Pct Total
2002 Q4	33	291	3604	8.07%
2003 Q4	40	428	4779	8.96%
2004 Q4	0	513	6268	8.18%
2005 Q4	0	515	6419	8.02%

246. Periodic Safety Update Reports (PSUR): Below is an overview of suicide-related adverse events (completed suicide, attempted suicide) found in a gabapentin PSUR covering the period from February 1, 2003 through January 31, 2004.[111] The PSUR documents include cases of adverse events reported spontaneously to Pfizer Defendants, cases reported from healthcare providers, cases published in the medical literature and cases reported from clinical studies, regardless of causality. Many of the cases noted below were published in the medical literature. A search of the database for additional PSUR documents was unsuccessful.

247. Gabapentin was listed as the sole suspect agent in a total of 6 completed suicides and 15 suicide attempts. In addition, there was one case of intentional self-injury where gabapentin was considered the sole suspect agent. Twelve cases of completed suicide and 7 cases of attempted suicide listed gabapentin as a co-ingestant. Note that on Page 5 of the PSUR document (under a section titled Death), 18 completed suicides are noted. Very limited information is provided about these cases. The 5 year PSUR document (reviewed previously) listed 12 and 14 cases of suicide and suicide attempt, respectively. These cases represent additional evidence that completed and attempted suicides continued to accumulate in postmarketing databases. Pfizer Defendants should have noted these events and taken the necessary steps to adequately warn patients and prescribers of the risks associated with gabapentin. As discussed in previous sections of this report, these changes should have included strengthened labeling language related to the suicide events.

[111] Pfizer_PSUR_0003596

Gabapentin Suicide-Related Events

February 1, 2003 - January 31, 2004 PSUR

Gabapentin as the Sole Suspect Agent

Completed Suicide (6)

Patient ID	*Age/Sex*
2003013657[1]	Unk
2003013658	Unk
2003016394[2]	54 Unk
2003017239	Unk M
2003113340	73 M
2004002253	Unk

Suicide Attempt (15)

Patient ID	*Age/Sex*
2003013675	Unk
2003013665	Unk
2003013666	Unk
2003013667	Unk
2003013668	Unk
2003013669	Unk
2003013670	Unk
2003013671	Unk
2003013672	Unk
2003013673	Unk
2003013674	Unk
2003018800	76 F
2003009454	45 M
2003118178 (Intentional Self-Injury)	65 F
2003030526	Unk F

[1] *Cases in **bold** were reported in the Journal of Toxicology and Clinical Toxicology (2003), 41(1):11-15.*
[2] *Cases in italics were reported in the American Journal of Emergency Medicine (2001), 19(5): 337-395 or (2003), 21(5): 353-421.*

Gabapentin Suicide-Related Events

February 1, 2003 - January 31, 2004 PSUR

Gabapentin Listed with Co-Ingestants

Completed Suicide (12)

Patient ID	*Age/Sex*
2003016387[2]	52 Unk
2003016395	19 Unk
2003016396	36 Unk
2003016397	54 Unk
2003016399	11 F
2003016415	21 Unk
2003016417	38 Unk
2003039719	54 Unk
2003039720	50 Unk
2003039721	34 Unk
2003039897	27 Unk
2003039898	52 Unk

Suicide Attempt (7)

Patient ID	*Age/Sex*
2003115804	52 F
2003116563	28 F
2003119634	Unk F
2004001909	48 F
2003041397	Unk
2003006078[1]	19 M
2003119930	Unk F

[1] *Cases in **bold** were reported in the Journal of Toxicology and Clinical Toxicology (2003), 41(1):11-15.*
[2] *Cases in italics were reported in the American Journal of Emergency Medicine (2001), 19(5): 337-395 or (2003), 21(5): 353-421*

Adverse Event Reporting System (AERS) Adverse Event Data

248. Adverse psychobiologic events occurring in individuals receiving gabapentin and reported to the Adverse Event Reporting System (AERS) database were analyzed. A number of signals associated with suicide-related events were apparent during the time period reviewed. Between 2002 and 2003 the number of completed suicides nearly tripled. This increase mirrored similar signals observed by Pfizer Defendants for psychobiologic adverse events. Events linked to suicidal behavior (depersonalization, depression) were also noted to occur in patients receiving gabapentin, demonstrating the potential serious psychobiologic effects of this drug and further confirming the necessity of an enhanced product label. By the end of 2005, completed suicide comprised over 3% of the total database. Cases of suicide attempt and suicide ideation also continued to increase, comprising 1.42% and 1.98% of the database respectively by the end of 2005.

Gabapentin Suicide-Related Events from the AERS Database 2002-2005

	2002 Q4		2003 Q4		2005 Q4	
Costart Term	**Reports[#]**	**%**	**Reports**	**%**	**Reports**	**%**
Completed suicide	27	0.42 %	75	0.79%	485	3.17%
Suicide attempt	73	1.13%	98	1.03%	217	1.42%
Suicidal ideation	55	0.85%	98	1.03%	303	1.98%

[#]Reports are cumulative and represent numbers received through the fourth quarter for each year.

Gabapentin AERS Psychobiologic Adverse Event Data (2002-2005)

	2002 Q4		2003 Q4		2005 Q4	
Costart Term	**Reports***	**Pct**	**Reports**	**Pct**	**Reports**	**Pct**
Abnormal Dreams	13	0.20%	18	0.19%	42	0.27%
Affect lability	6	0.09%	6	0.06%	20	0.13%
Aggression	45	0.70%	67	0.71%	124	0.81%
Agitation	81	1.26%	127	1.34%	236	1.54%
Anxiety	117	1.82%	229	2.41%	459	3.00%
Completed suicide	**27**	**0.42%**	**75**	**0.79%**	**485**	**3.17%**
Confusional state	246	3.82%	370	3.90%	603	3.94%
Delirium	41	0.64%	56	0.59%	99	0.65%
Delusion	18	0.28%	24	0.25%	49	0.32%
Depersonalization	12	0.19%	15	0.16%	17	0.11%
Depression	186	2.89%	309	3.25%	614	4.01%
Hallucination	86	1.33%	132	1.39%	209	1.37%
Hostility	40	0.62%	43	0.45%	54	0.35%
Intentional self-injury	4	0.01%	7	0.07%	26	0.17%
Major depression	9	0.14%	15	0.16%	27	0.18%
Nervousness	58	0.90%	83	0.87%	139	0.91%
Overdose	130	2.02%	183	1.93%	384	2.51%
Paranoia	26	0.40%	43	0.45%	66	0.43%
Personality disorder	13	0.20%	18	0.19%	27	0.18%
Psychotic disorder	66	1.02%	80	0.84%	116	0.76%
Suicidal ideation	**55**	**0.85%**	**98**	**1.03%**	**303**	**1.98%**
Suicide attempt	**73**	**1.13%**	**98**	**1.03%**	**217**	**1.42%**
Thinking abnormal	46	0.71%	65	0.68%	103	0.67%
Death	93	1.44%	141	1.48%	199	1.30%

World Health Organization (WHO) Adverse Event Data

249. Adverse psychobiologic events associated with gabapentin and reported to the World Health Organization (WHO) between 2002 and 2005 were compiled and are presented below (see table). Of note, suicide attempts were the third most frequently-reported adverse psychiatric event, and they increased by more than 3-fold between 2002 and 2003. Other events considered precursors to suicide-related behavior (depression, depersonalization) also increased dramatically in 2005. These elevated numbers of adverse psychobiologic events should have come as no surprise to Pfizer Defendants, as these trends mirrored effects observed even prior to gabapentin approval. These types of adverse psychobiologic events were also observed in additional Postmarketing databases including the Pfizer Defendants' internal database and the AERS database.

World Health Organization

Top 25 Psychiatric Adverse Events (2002-2005)

Adverse Reaction	2002	2003	2004	2005	Cumulative Total (since 1993)
Somnolence	37	56	41	90	496
Confusion	26	49	25	57	276
Suicide Attempt *	***13***	***48***	***42***	***96***	***249***
Amnesia	11	25	11	47	178
Depression	3	27	14	56	152
Aggressive Reaction	5	15	9	37	152
Hallucination	8	23	13	27	144
Depersonalization	5	10	17	62	142
Insomnia	6	20	16	40	133
Anxiety	8	14	15	47	123
Agitation	4	20	7	35	118
Nervousness	5	6	13	21	111
Drug Abuse	9	11	8	11	103
Personality Disorder	3	4	10	34	94
Emotional Lability	6	13	12	22	86
Thinking Abnormal	7	12	8	13	66
Psychosis	3	8	5	19	64
Anorexia	4	9	2	23	63
Impotence	3	6	6	9	57
Drug Dependence	5	13	7	20	50
Concentration Impaired	0	4	8	13	47
Mental Deficiency	5	3	3	5	43
Sleep Disorder	4	5	6	12	35
Libido Decreased	2	2	4	5	31
Paranoid Reaction	2	7	1	3	31

* *Intentional Overdose was not included under this term until late 2004*

GABAPENTIN – FOREIGN REGULATORY EVENTS

250. A number of foreign regulatory events concerning gabapentin demonstrate that safety was a concern for this drug not only in United States patients but also worldwide.

251. Netherlands Medicines Evaluation Board (April 9, 2003). The Netherlands MEB submitted an assessment report on gabapentin to Pfizer Defendants stating that sudden death, off-label use of gabapentin in treating bipolar disorders, manic episodes due to gabapentin (and other adverse events) should be discussed in the next PSUR.[112] Additional items were also noted but are not discussed here. In response to this query, Pfizer Defendants noted (in an internal document) that they would monitor and discuss sudden death, off-label use of gabapentin in treating bipolar disorders and manic episodes following use of gabapentin in the next PSUR (February 1, 2003 through January 31, 2004). Pfizer Defendants did provide discussion for each of these topics in the noted PSUR document.

252. Investigator's Brochure Addendum for Epilepsy Studies in Japan (July 2004). This document lists a total of 3 reports of completed suicide occurring in the overall gabapentin development program (data were current as of May 24, 2004). The cause for 2 of these events was listed (cervical vertebral fracture, intentional overdose). Other serious psychobiologic adverse events occurring in Japanese studies are also listed (psychiatric symptom aggravated, panic disorder). These reports further demonstrate the serious psychobiologic adverse events associated with gabapentin and the need for strengthened wording in the label relating to these risks. Note that the Japanese Investigators brochure lists 3 suicides associated with gabapentin while the September 2004 submission to the FDA listed only 2 completed suicides. This discrepancy may result from differences in the reporting period between the two documents.

253. Australian Therapeutic Goods Administration (TGA) (September 4, 2003). Following review of a 5 year gabapentin PSUR document (February 1, 1998 through January 31, 2003), the Australian Therapeutic Goods Administration (TGA) recommend a number of gabapentin labeling changes.[113] These include addition of the following terms: anxiety (based on 93 reports); hallucinations (94 reports); depersonalization (56 reports); and psychosis (40 reports). It is unclear whether these events were incorporated into the Product Information sheet. Pfizer Defendants addressed these concerns in a submission dated December 4, 2003.

254. German inquiry on suicide (September 10, 2004). Pfizer Defendants received an inquiry from the "arznei-telegramm" (Drug Telegram) requesting the number of reports of "suicidal tendency, suicidal ideation or (attempted) suicides…" associated with gabapentin.[114] The author also requested clarification as to why the adverse event terms "suicidal" and "suicide gesture" were included in the gabapentin United States Product Information (label) but were not mentioned in the German Product Information. Pfizer Defendant internal emails discussing this inquiry note that the

[112] *See* Pfizer_THO_0000746
[113] *See* Pfizer_THO_0008296-300
[114] *See* Pfizer_THO_0001538-41

reason for inclusion of these terms (suicidal and suicide gesture) in the US label but not in the German label is the difference in the approach to adverse events taken by each country. The following is quote from an email dated September 13, 2004:

> In US, all AEs (whether or not related to the drug) have been listed in the USPI whereas the European approach is to list only relevant information (with at least possible drug relationship), thus the IPI reflects only the AEs that were considered revelant [sic].[115]

255. Based on this statement, the US label should have contained the adverse event terms "completed suicide" and "suicide attempt". Up to that point in time, numerous reports of suicide and suicide attempt had been reported to various postmarketing databases, published in the medical literature and discussed in Pfizer Defendant-prepared documents such as PSURs and Safety Updates. Indeed, the FDA submission noted 12 cases of suicide attempt and 2 completed suicides; despite this, the US labeling contained no information on these risks, instead listing only the generic terms suicidal and suicide gesture. Pfizer Defendants have recently updated the US Neurontin label to reflect suicide and suicide attempt in clinical trial patients receiving gabapentin.

256. Medical Literature: A review of published medical literature during the period under review in this section of the report reveals cases of completed or attempted suicide and/or overdose associated with Gabapentin. Included below for reference are pertinent citations:

1. Klein-Schwartz et al. (2003) **Characterization of gabapentin overdose using a poison center case series**, *Journal of Toxicology and Clinical Toxicology*, 41(1): 11-15.

- **Design:** Multicenter, Prospective, Observational Study
- **Dates of study:** 4/1/98- 4/1/00
- Gabapentin exposure cases obtained from 3 poison centers evaluated with regard to age, gender, reason, dose ingested, chronicity, management site, treatment, clinical effects, duration of clinical effects, and medical outcome.
- Cases were excluded because of reports of coingestants or because of unknown final management site or unknown medical outcome.
- **77 cases reported**
  - 52 excluded due to co-ingestants
  - 5 excluded due to unknown medical outcome or management site

[115] *See* Pfizer_THO_0001538-41

- **20 (of 77) cases reported as gabapentin-only**
  - Age range: 11 months to 83 years (50% < 19 years old)
  - Intentional suicide reported for 55% of the cases
  - 65% of the exposures were acute-on-chronic
  - No deaths occurred

2. Watson et al. (2003) **2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System**, *American Journal of Emergency Medicine*, 21: 353-421.

3. Watson et al. (2004) **2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System**, *American Journal of Emergency Medicine*, 22: 335-404.

4. Watson et al. (2005) **2004 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System**, *American Journal of Emergency Medicine*, 23: 589-666.

257. Available data from the 2002-2004 Annual Reports of the American Association of Poison Control Centers were reviewed for suicide-related events. Data contained in these reports, which include a listing of primary and suspect medications in the case of overdoses, were obtained from poison control centers in the US and published in the American Journal of Emergency Medicine. From these reports, 24 instances of a poisoning death in which a patient was taking gabapentin were found. Eighteen of these reports were intentional overdoses; the remaining 5 were for either unknown or adverse reaction reasons.

258. Although Pfizer Defendants did discuss with FDA the requirements necessary for obtaining OTC approval for use of gabapentin as a sleep enhancing agent in 2003, Pfizer Defendants received no new indications for gabapentin during the period covered by this section of PDG's evaluation (June 2002 through 2006). Pfizer Defendants did receive FDA approval for pregabalin (Lyrica), a drug similar to gabapentin, in December of 2004. Lyrica is indicated for the treatment of epilepsy (add-on therapy), neuropathic pain associated with post herpetic neuralgia, neuropathic pain associated with diabetic peripheral neuropathy, and fibromyalgia Of note, the product labeling for Lyrica contained the terms suicide and suicide attempt to reflect the occurrence of these events during pre-marketing clinical trials. Pfizer Defendants did not perform a similar action for gabapentin for more than 12 years.

259. During the period reviewed for this section of the report (June 2002 – 2006) Pfizer Defendants continued to reap the benefits of off-label gabapentin use. A recent publication reviewed efforts utilized by Pfizer Defendants to promote gabapentin for

use in unapproved conditions and underscored the extent to which profits were prioritized over demonstrations of efficacy and safety.[116] A large percentage of this off-label use likely occurred in patient populations at risk of adverse psychobiologic events, including patients with various mood disorders and those experiencing generalized neuropathic pain.[117] Despite this off-label use in susceptible populations and the continuing accumulation of postmarketing reports of suicide-related events in their internal database, Pfizer Defendants did not update their gabapentin label to include the terms "suicide" and "suicide attempt" until May 2006 and only following FDA requests for information on suicide events. Furthermore, these changes were incorporated only into the section discussing events observed in clinical trials. The vast numbers of postmarketing suicide-related events continue to be ignored, depriving patients and prescribers of adequate risk/benefit information.

260. Pfizer Defendants submitted to FDA their analysis of suicide-related events in September 2004. Despite the occurrence of 12 suicide attempts and 2 completed suicides in patients participating in gabapentin clinical studies, Pfizer Defendants felt no need at that time (September 2004) to update the label to include these terms. This change was ultimately made in May 2006, following an additional request by FDA to analyze suicide events occurring in controlled clinical trials (March 2005). Unfortunately, this critical update to the product label, providing prescribers (and patients) with a more "real world" view of adverse events occurring in subjects receiving gabapentin, was not made. As more homogeneous populations are typically observed in pre-marketing clinical trials, one cannot expect a similar adverse event profile following use in the general population, particularly with a drug such as gabapentin which enjoys a high percentage of off-label use. Furthermore, many of these off-label patient populations are at increased risk for suicidal behaviors, a situation that should have prompted Pfizer Defendants to provide adequate suicide-related warnings in the gabapentin label.

261. Pfizer Defendants could have performed a review similar to that requested by FDA at a much earlier time point. The recent label changes (May 2006) were apparently (at least partly) based on data provided to FDA in September 2004 (2 completed suicides and 12 suicide attempts). Interestingly, as all of these events occurred prior to September 2000, one has to wonder why Pfizer Defendants did not consider it appropriate to update the gabapentin label at that time. Had Pfizer Defendants performed the necessary pharmacovigilance and appreciated the increasing numbers of postmarketing events of suicidal behavior, observed in their own internal database as well as the US and foreign (WHO) databases, and medical literature, perhaps the appropriate label changes could have been made earlier. Unfortunately, this did not occur.

262. Pfizer Defendants had been warned in 2005 about failing to provide important information in a print advertisement relating to the risk of suicidality in patients taking Zoloft. FDA noted that the omission of this information was "…concerning from a public health perspective because it fails to include a serious risk associated with the drug."[118] A similar situation exists with gabapentin. Important information

[116] Steinman et al., 2006
[117] Hamer et al., 2002
[118] Letter from Kay Chitale (DDMAC) to Mojgan Moghadassi (Pfizer); May 6, 2005

about the risks associated with the drug are not prominently noted in the label, as they should be.

V. PFIZER DEFENDANTS FAILED TO ADEQUATELY ASSESS AND TAKE APPROPRIATE ACTION REGARDING RISKS OF SUICIDAL BEHAVIOR ASSOCIATED WITH USE OF NEURONTIN.

263. As mentioned previously, abundant information relating to drug safety in a variety of populations is not available when a new drug product is first marketed. Pre-marketing clinical trials are designed to demonstrate efficacy and usually only provide information concerning the most common side effects (e.g., dizziness, somnolence) because the employed populations are relatively small and inadequate to detect the more infrequently occurring events. Following FDA approval and use of the drug in a broader population for longer periods, additional safety concerns may arise. It is critical that these events, particularly the serious and potentially fatal events (such as those related to suicidal behavior) are monitored closely and that appropriate risk information is provided immediately to patients and prescribers. As noted earlier, this is especially critical for patient populations that may be more vulnerable to the observed adverse event. Manufacturers may provide this information in numerous formats including Dear Dr. letters, new labeling changes and promotional materials.

264. Pfizer Defendants have repeatedly utilized case reports of Neurontin efficacy in off-label indications (e.g., psychiatric conditions, neuropathic pain, migraine, sleep) to initiate further investigations. Conversely, a similar process has not been followed for case reports describing serious psychobiologic adverse events, including those related to suicide (see below for a list of case reports describing suicidal behavior in subjects taking Neurontin). Pfizer Defendants have chosen to either ignore these adverse events or provide mitigating factors such as other drug use, patient history or the background rate of the event in subpopulations.

265. In the U.S., Neurontin has been approved for use only in a relatively restricted set of patients (e.g., epileptics and patients with neuropathic pain associated with post herpetic neuralgia). Unrestrained off-label use of Neurontin resulted in the exposure of numerous patient populations to a drug demonstrated to produce a constellation of psychobiological adverse events, including psychosis, depression, suicide attempts and completed suicide. An especially cruel consequence to Pfizer Defendants' illegal activities was that the most vulnerable populations (bi-polar and other psychiatric disorders, chronic or unresolved pain) were exposed to Neurontin and these dangerous self-injurious and auto-aggressive side effects. Additionally, Pfizer Defendants failed to reasonably warn healthcare professionals and patients as to the lack of proven efficacy in off-label uses, even though Pfizer Defendants illegally promoted Neurontin on an off-label basis. Even in the absence of such off-label promotion, Pfizer Defendants knew about and financially benefited from the overwhelming off-label use of Neurontin and suppressed information as to Neurontin's lack of efficacy.

266. Because the vulnerable patient populations noted above (bipolar and other psychiatric disorders, chronic or unresolved pain) are at increased risk for suicide-

related behavior, it is imperative that they (and their prescribers) are fully cognizant of adverse events that may occur following use of Neurontin. Had Pfizer Defendants chosen to adequately address the significance of the growing numbers of common psychobiological adverse events (including those related to suicide) observed during clinical trials and reported in Pfizer Defendants' post-marketing databases, through amplifications of the product labeling and/or warning letters to physicians, many of these events could have been avoided. Indeed, the July 1996 letter from the FDA represented an opportunity for Pfizer Defendants to mitigate the off-label uses of Neurontin and thereby reduce the risk to these susceptible populations.[119] Unfortunately, Pfizer Defendants did not take any action and allowed the risk to these vulnerable populations to continue without adequately warning these populations of the risks.

267. Manufacturers have frequently attempted to utilize a "causation argument" to shield their inadequate actions, or inaction, from liability for not providing adequate warnings to consumers or their prescribers. However, as plainly articulated above, *causation* is not a required element before a reasonable manufacturer takes the necessary action to either incorporate an adverse event term into a drug label or send a Dear Doctor letter warning of the risk. In reality, if *causation* were required, patients and prescribers would be needlessly imperiled by delays in receiving critical safety information, assuming that the innovator would even choose to conduct such causation studies.

268. For example, as noted in the Code of Federal Regulations (21 C.F.R. § 201.57) a causal relationship need not have been proved or definitely established in order to revise a warning in the drug product label.[120] The FDA has also provided similar statements on multiple occasions, including when changing the label for diphenhydramine-containing products; "*Mandating a warning does not require a finding that … drug products contain[ing] diphenhydramine actually caused an adverse event, and FDA does not so find."* (Federal Register, Vol. 67, No. 235; p. 72556, Dec 6, 2002). Later in the same document, FDA noted that *"[t]o mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation."* (Federal Register, Vol. 67, No. 235; p 72556, Dec 6, 2002). FDA

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[119] *See* WLC_FRANKLIN_0000053292-53300; correspondence from Lesley R. Frank, Ph.D., J.D., Special Assistant to the Dir. Division of Drug Marketing, Advertising and Communications (FDA, CDER) July 19, 1996.

[120] 21 CFR 201.57 (2007) provides that a product's "labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established". Noteworthy, Defendant Pfizer's witness, Manfred Hauben (Medical Director of Risk Management Strategy for Pfizer) was produced by Pfizer Defendants as a person to specifically address issue of pharmacovigilance by Defendants. Witness Hauben defined the purpose of his Risk Management Strategy Department as follows: "Its to detect, understand, identify and take appropriate mitigating and management activities to --- to manage risks associated with the use of medicines." Deposition of Manfred Hauben, July 12, 2007 at pp. 9-10. Yet, he did not know there was a distinction between causal association and causal relationship. *See* Deposition of Manfred Hauben, July 13, 2007, at p.506-507. "Q. And in terms of your knowledge, speaking here on behalf of the companies is there a distinction between a causal relationship and a causal association, when you're trying to determine whether an adverse event is attributable to Neurontin such as a psychiatric adverse event? A. Are you asking just in terminology used in discussions, would the word "a causal association" be equivalent to "a causal relationship"? Q. Yes. A. I would say yes."

also approved a recent (November 2005) change to the product labeling for Mifeprex® (US Food and Drug Administration, Questions and Answers on Mifeprex® (Mifepristone), November 4, 2005) to convey information regarding fatal bacterial infections in patients (four total) taking the drug. FDA specifically noted that a causal relationship between Mifeprex® use and these fatal infections had not been established. Thus, the absence of a well-controlled study demonstrating a difference in suicide rates between Neurontin and placebo-treated patients does not negate the importance of the additional factors (spontaneous postmarketing reports, case reports, biologic plausibility, dechallenge and rechallenge reactions) all suggesting a link between the drug and suicidal events.

269. There are various other drugs with stronger suicide warnings in their label despite the fact that the innovators of the drugs performed no controlled clinical trials designed to demonstrate "causation" differences between adverse event frequencies in the placebo and treated groups. For example, FDA noted that evidence of causation was not required to determine risk-benefit assessments or effect labeling changes related to suicide events associated with the acne medication Accutane.[121]

270. Pfizer Defendants, as the innovators and marketers of Neurontin, were responsible for conducting any studies that would be considered to be critical determinants of safety. Of course, it is nearly impossible (as well as unethical) to conduct a clinical study designed with suicide as the expected outcome.[122] Moreover, the number of patients required to detect the difference between an adverse event incidence of 1/10,000 versus 2/10,000 with 90% power would be >300,000 for both the treatment and control groups.[123] Given that most New Drug Applications (NDAs) contain information on drug effects in no more than 3000 patients, and Neurontin was

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[121] *See* www.hhs.gov/asl/testify/t001205.html for statement of Jonca Bull, M.D., (FDA, Deputy Office Dir. of the Center for Drug Evaluation and Research (CDER)), on December 5, 2000, at which time she discussed incoming adverse event reports of suicide with Accutane: They "were not numerous relative to the rate of depression and suicide expected to be seen in the population likely to receive Accutane, namely teens and young adults (sometimes referred to as the 'background rate'). Some of the reports, however, included important details that did suggest the possible involvement of Accutane. Some reports described a consistent pattern of symptoms in patients with no previous history of such symptoms and no other identifiable reason for their occurrence. Other cases were described in which the symptoms began during the Accutane treatment and then resolved soon after the medicine was stopped. In a subset of these cases, Accutane was then restarted and the same symptoms returned. While these findings do not prove that Accutane causes psychiatric illness, they are suggestive of a possible link."

[122] *See* statement by Janet Woodcock, FDA, Dir. Of the Center for Drug Evaluation and Research (CDER); December 11, 2002 before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce, US House of Representatives), at www.fda.gov/ola/2002/accutane1211.html. "This groundwork is of particular importance in the case of research on isotretinoin and psychiatric adverse events because there are a number of very significant technical and ethical problems with the type of trial usually conducted to settle causality questions (*i.e.*, a large randomized controlled trial). These problems arise because the drug is already on the market and recruitment of patients with scarring acne for a controlled trial would be very difficult and poses ethical questions…. Obviously, we cannot do a study where suicide is the endpoint; the less objective, but related, psychiatric endpoint, depression, is a problem because patients already know this drug works, and patients in the study would ethically have to need the treatment. Thus, there would be a large incentive to hide psychiatric symptoms in order to avoid being discontinued from the study, again greatly increasing the chance of a false negative result. This is particularly worrisome because such a result could likely seriously undermine the progress made to date in education and awareness".

[123] Wardel *et al.,* 1979, J Clin Pharmacol, 19(4), 169-184

approved based on data from 2074 patients (Neurontin Summary of basis approval, X023722), this number is far too restrictive to be practical. The FDA has repeatedly stated that it is "…impossible to identify all safety concerns during clinical trials" and that post-marketing data are "…critical for evaluating and characterizing a product's risk profile.…"[124] As correctly noted by the Defendants, drug labeling "*...must fully apprise doctors of known risks associated with the drug."*[125]. However, as noted below, these risks can be determined from multiple sources and are not exclusive to those occurring during clinical trials, a fact that has been reiterated by FDA on numerous occasions. Thus, the fact that there is no clinical trial data on the issue of suicide and Neurontin does not equate to a lack of an association. However, many types of epidemiology trials and prescription database evaluations are available to assess infrequently-occurring postmarketing adverse events.

271. One should never denigrate the value of post-marketing adverse event reporting. Adverse event reports form the basis of post-marketing labeling changes, use restrictions and even market withdrawal of a drug. Indeed, a study examining information utilized to withdraw medicinal products from either the United States or United Kingdom markets during the period 1999-2001 found that a total of 11 products were withdrawn during this period.[126] Evidence from spontaneous (postmarketing) reports supported the withdrawal of 8 of these products and 4 products were apparently withdrawn based solely on spontaneous reports.[127] Thus, because post-marketing reports are sufficient for removing a product from the marketplace, it is obvious that these could support a labeling change to increase safe product use.

272. FDA defines a safety signal as "*a concern about an excess of adverse events compared to what would be expected to be associated with a product's use"*.[128] FDA specifically states that these signals can arise from post-marketing data (as well as other sources) and that "…*even a single well-documented case report can be viewed as a signal.…"*[129] Thus, the notion that clinical trials are the gold standard for detection of adverse events is a fallacy, primarily because they are typically not designed to detect rare adverse events.[130]

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[124] *See* Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA, March 2005.

[125] Pfizer, Inc., Motion for Summary Judgment, July 25, 2006 at p. 16.

[126] Clarke, et al., 2006

[127] Clarke, et al., 2006

[128] Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA, March 2005.

[129] Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA, March 2005; *see also* NDA20235_MISC_002_080, entitled Parke-Davis Worldwide Regulatory Affairs FDA Contact, dated February 11, 1998, in which it states, "Dr. Katz [at FDA] began the teleconference by describing their philosophy for inclusion of specific adverse events. Their threshold for including adverse events [in the package insert] is fairly low because it is hard to determine causation from either the report or the frequency of the report. Thus, their general rule is to add even a single report if it is a 'half way decent' report with no obvious reason not to include it. They prefer to list the report and let the reader be the judge."

[130] *See* Dep. of Pfizer Defendants' witness, Manfred Hauben (Medical Dir. of Risk Management Strategy) (July 12, 2007) at p.194-195. "Q. Do you agree or disagree that premarketing trials are rarely large enough to detect small differences in the risk of common adverse events or to reliably estimate the risk of rare events? . . . A. Generally, clinical trials are not --- are not powered to detect --- rare events . . . ." *See also*

273. Although it is impossible to design a clinical study and unethical to design a clinical study to demonstrate that Neurontin causes suicide, there are several factors that contribute to a determination of the causality of an event including: the temporal relationship of the adverse event to drug ingestion; positive dechallenge/rechallenge events, biological plausibility of the event in relation to the mechanism of action of the drug and the frequency of the event. Indeed, there is one instance of a patient expressing suicidal ideation which subsided following tapering of Neurontin (*i.e.,* a dechallenge; see Research Report # 720-02837). This patient also experienced a positive rechallenge (re-occurrence of the adverse event following discontinuation and subsequent reinstatement of the drug) for depression. These types of events represent evidence that the drug may have caused (or is associated with) the adverse event. As noted by FDA, "[i]*t is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use."*[131]

274. Numerous instances of positive dechallenges can be found in patients experiencing psychobiological adverse events following Neurontin use (see Research Report #s 720-03498; 720-0389; 720-03893; 720-04363; 720-04232; 720-03894; 720-02837). Pfizer Defendants should have examined these events more closely to determine their relationship to Neurontin, particularly as the drug gained wide acceptance for use in non-indicated conditions such as bipolar disorder and neuropathic pain. Some of these psychobiological events (depression, depersonalization) are believed to contribute to suicide-related behavior (Kelly and Knudson, 2000), a finding which reinforces the importance of providing patients and prescribers with appropriate risk-benefit information.

275. A Safety Update Document prepared by Pfizer Defendants discussed the issue of behavior-related events (psychosis) occurring during the period 1998-2003 (Pfizer, Periodic Safety Update Report, March 21, 2003). Out of a total of 40 reports of psychosis, 7 cases demonstrated a positive dechallenge. Pfizer Defendants admitted that a causal effect of gabapentin in these cases "*could generally not be completely excluded".* These cases represented yet another signal of the psychiatric effects associated with Neurontin and presented an opportunity to Pfizer Defendants to further study the more serious adverse events related to psychiatric conditions (including suicide and suicide-related behaviors) and to update the product label to reflect these risks.

276. Controlled clinical trials performed in support of the efficacy of Neurontin also demonstrate the potential suicide risks. Indeed, Pfizer Defendants were asked by FDA to perform an analysis of suicide-related events occurring during clinical trials with Neurontin. In September 2004, Pfizer Defendants submitted to FDA an analysis of suicide attempts and completed suicides occurring in all Phase I-Phase IV trials (predominantly trials in epileptic patients and patients with neuropathic pain) performed with Neurontin. Their analysis showed that there were 12 instances of

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Dep. of Pfizer Defendants' witness, Manfred Hauben (Medical Dir. of Risk Management Strategy) (July 12, 2007) at p.253. "Q. Are you familiar with the theory called the Rule of 3s? A. Yes. Q. Can you explain it to us? A. Yes. If you have something with an incidence of, say, one in a thousand, to be 95 % confident of observing one or more cases, you would want to -- you'd have a series of 3000 people."

[131] Guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

suicide attempt and 2 cases of completed suicide in patients receiving Neurontin. Patients treated with placebo during these trials evidenced no instances of either suicide attempt or completed suicide, a finding that refutes assertions of higher background rates of suicide-related behavior (Response to FDA Regarding Suicide and Suicide Attempt in Neurontin (gabapentin) Clinical Trials and Postmarketing Surveillance). Thus, while it is generally agreed that epileptic patients have elevated rates of suicidal behavior (Jones et al, 2003), the finding that *all* suicide-related events occurred in patients treated with Neurontin represented a pharmacovigilance signal that should have been acted on by Pfizer Defendants. Moreover, FDA has rejected the comparison of self-injury and suicidal pharmacovigilance data with baseline data from a demographically similar untreated population as a method to avoid complete disclosure of suicide-related events (Accutane, FDA Alert for Healthcare Professionals; November 2005).

277. Pfizer Defendants did acknowledge the occurrence of suicide and suicide attempt in Neurontin clinical trials in a label change submitted by Pfizer Defendants in December 2005 and enacted in May 2006. This label change was prompted by an FDA request to analyze suicide-related events occurring in controlled clinical trials. **Of note, this change to reflect suicidal behavior was affected only in the section related to adverse events occurring in clinical trials and not in the post-marketing section.** This action ignores the vast numbers of post-marketing report of suicide events, some of which are likely to have occurred in patients receiving the drug for off-label indications.

278. Although the FDA did approve the Neurontin labeling after review of the suicide-related events, the lead reviewer (NDA #20-235 Medical-Statistical Review at p.117) noted that certain risks associated with the drug, including *"clinically important depression"*, were yet to be *"fully characterized"* (NDA #20-235 Medical-Statistical Review at p.117). She also noted that the risk profile for Neurontin was *"uncertain*" (NDA #20-235 Medical-Statistical Review at p.117) and that the drug should only be used in a *"specific population"* and associated *"prominent labeling"* (NDA #20-235 Medical-Statistical Review at p.119).

279. Soon after receiving approval from the FDA for the adjunctive treatment of epilepsy (December 1993), Neurontin use in the treatment of a number of off-label indications (bipolar disorder, neuropathic pain) greatly increased secondary to the Pfizer Defendants' efforts to promote off-label use. As many of these conditions involved patients at increased risk of suicidal behaviors, Pfizer Defendants (then Parke-Davis) should have realized the potential risks involved (based upon suicide-related behavior observed in the epilepsy studies) and taken steps to warn all patients of the associated suicide-related risks.

280. Additional lines of evidence reflecting an association between Neurontin and suicide-related events include case reports and post-marketing databases. Indeed, there are numerous examples of uncontrolled studies (case studies, case reports) that demonstrate an association between Neurontin and suicidal behavior, including reports of attempted suicides (intentional overdose) as well as suicide. While these events do not prove that Neurontin causes suicidal behavior, they do demonstrate, in conjunction with the vast numbers of post-marketing events, that Neurontin can be

associated with suicide-related behavior and that appropriate warnings should be provided to patients in order to mitigate against these events.

281. Pfizer Defendants still have not conducted a controlled clinical or epidemiological study designed to assess whether there is a significant difference in suicide-related events in patients taking Neurontin, but that does not mean that case reports of such events have no value. A review of the medical literature reveals several articles discussing suicide-related events in patients receiving Neurontin. It is important to note that the Pfizer Defendants did not initiate theses studies, alert the public of their publication or follow-up on any of the published results. Below, a list of medical literature describing suicidal behavior in patients receiving Neurontin is provided. In several cases, there was no listing of additional drugs, a finding that lends additional weight to Neurontin producing these events in certain individuals.

1993 Garofalo E, Koto E, and Feuerstein T, **Experience with gabapentin overdose: Five case studies**, *Epilepsia,* 34: 157.

1996 Fernandez MC, Walter FG, Petersen LR et al., **Hemodialysis and hemoperfusion for treatment of valproic acid and gabapentin poisoning,** *Vet Hum Toxiccol,* 38: 438-443.

1996 Fernandez MC, Walter FG, Petersen LR et al., **Gabapentin, valproic acid, and ethanol intoxication: elevated blood levels with mild clinical effects,** *J Toxicol Clin Toxicol,* 34: 437-439.

1997 Stopforth J, **Overdose with gabapentin and lamotrigine,** *S Afr Med J,* 87: 1388.

2001 Mathews SC and Dimsdale JE, **Priapism after a suicide attempt by ingestion of olanzapine and gabapentin,** *Psychosomatics,* 42: 280-281.

2002 Spiller HA, Dunaway MD, and Cutino L, **Massive gabapentin and presumptive quetiapine overdose,** *Vet Hum Toxicol*, 44: 243-244.

2002 Paopairochanakorn, C, White, S, and Malafa, MJ, **Cardiac and Neurologic Toxicity from Lamotrigine Ingestion,** *J Toxicol Clin Toxicol,* 40: 620-621.

2003 Klein-Schwartz W, Shepherd JG, Gorman S et al., **Characterization of gabapentin overdose using a poison center case series,** *J Toxicol Clin Toxicol,* 41: 11-15.

Klein-Schwartz et al. examined 20 cases of overdose with gabapentin (Neurontin). Eleven (11) of these cases were intentional suicide attempts.

2005 Moore KA, Levine B, and Fowler D, **A fatality involving metaxalone,** *Forensic Sci Int,* 149: 249-251.

282. While these do not represent the "gold standard" studies, which Pfizer Defendants failed to conduct even though it was clear that adverse event safety signals were evident even prior to the original marketing of Neurontin**,** they demonstrate that suicide-related events occur in subjects receiving Neurontin. Furthermore, given the well-known effect of under-reporting of adverse events, this suggests that many more similar type events may occur yet not be realized by the medical community.

Journal of Affective Disorders (2007):
Significant Increased Risk of Suicide with Gabapentin vs. Lithium

283. Despite Pfizer Defendants' failure to sponsor an appropriate controlled clinical or epidemiological study designed to assess whether there is a significant difference in suicide-related events in patients taking Neurontin, there does exist in the literature such information. Authors Jon Collins and Bentson McFarland presented an article entitled, **Divalproex, lithium and suicide among Medicaid patients with bipolar disorder**, in the Journal of Affective Disorders (2007). The authors recognized an increased risk of completed suicide in those patients exposed to gabapentin as compared to lithium.[132]

284. Collins and McFarland "examined relationships between suicidal behavior and medication use for Medicaid patients with diagnoses of bipolar disorder. The objective was to compare rates of completed suicide and suicide attempts among those Medicaid patients using lithium, divalproex, and/or other anticonvulsant medications, with emphasis on the initial (or index) episode of medication use during the study period."[133]

285. Having identified subjects from Oregon's Medicaid and mental health databases, the authors evaluated completed suicide and emergency department visits related to suicide attempts. Out of 12,662 subjects in said databases, gabapentin subjects equaled 4,025 (31.8%) of the total population. There were observed two suicides among lithium users (3,200 subjects), two among divalproex users (4,142 subjects), seven among gabapentin users (4,025 subjects), and none in the carbamazepine group (420 subjects).[134] The chart below reflects exposures and events as reflected by Collins and McFarland:

[132] *See* J.C. Collins, B.H. McFarland, *Journal of Affective Disorders* (2007). "Funding for this study was provided by Abbott Laboratories, which had no further role in study design; in the collection, analysis and interpretation of data; in writing of the report; and in the decision to submit the paper for publication." *Ibid.*
[133] J.C. Collins, B.H. McFarland, **Divalproex, lithium and suicide among Medicaid patients with bipolar disorder,** *Journal of Affective Disorders* (2007).
[134] J.C. Collins, B.H. McFarland, **Divalproex, lithium and suicide among Medicaid patients with bipolar disorder,** *Journal of Affective Disorders* (2007).

Table 2
Exposures and events

	Lithium	Divalproex	Gabapentin	Carbamazepine	Total
Total person-years of exposure	2558	2214	2002	242	7017
Completed suicides	2	2	7	0	11
Suicide attempts	15	41	19	4	79
Completed suicides per thousand person-years of exposure	0.78	0.90	3.50	0.00	1.57
Suicide attempts per thousand person-years of exposure	5.86	18.52	9.49	16.51	11.26

Note: Analyses excluded subjects who used lamotrigine, oxcarbazepine, or combinations of mood stabilizers. The excluded subjects accounted for two suicide attempts and one completed suicide.

286. Collins and McFarland provided hazard ratios for the divalproex, gabapentin, and carbamazepine users, respectively, versus lithium users as the reference group. "The adjusted hazard ratio for completed suicide among divalproex users was 1.5 but this elevated risk of suicide death was not statistically significant. However, risk of suicide completion was significantly (2.6 times) greater among gabapentin users versus lithium users (*p* less than 0.001)"[135] As noted earlier in this report, FDA has instructed manufacturers that safety signals cannot be minimized or dismissed based on a reliance of background incidence rates. Similarly, NDA sponsors must amend product labeling to reflect new safety signals notwithstanding background incidence rates.

Comparing Neurontin's Labeling to other Anti-epileptic Drugs

287. A comparison of the gabapentin labeling to that of other antiepileptic agents reveals that the wording relating to suicide is deficient for gabapentin. In fact, wording related to suicidal behavior in the gabapentin label has not changed over the lifetime of the drug's approval until its minor revision in 2006. The initial label, (January 1994) lists the term "suicidal" as an *infrequent* event and the generic term "suicide gesture" as a *rare* event observed in all clinical trials. Labeling for gabapentin (revised February 2005) contains identical wording in relation to the suicide events despite the growing number of suicide attempts and completed suicides in patients receiving gabapentin.

288. Following a request by FDA to examine suicide-related events in their controlled clinical trials (March 2005) Pfizer Defendants belatedly corrected the Neurontin label to reflect the incidence of suicide and suicide attempts during these trials. Importantly, Pfizer Defendants' label change to add suicide and suicide attempt to the product labeling was based upon information that existed in part since the drug's pre-marketing clinical trials. In contrast, another Pfizer Defendants product (Lyrica®) noted the occurrence of suicide and suicide attempt in the label at product launch, reflecting the occurrence of these events during clinical trials although there was only one event of suicide and three events of suicide attempt.

289. Other antiepileptic agents contain enhanced warnings in their product labeling related to suicide including Keppra® and Zonegran®. The labeling for Zonegran® (Elan Biopharmaceuticals, approved March 2000) provides a comparison of the percentage of placebo (0.4%) versus Zonegran® (1.1%) patients attempting suicide in

[135] J.C. Collins, B.H. McFarland, **Divalproex, lithium and suicide among Medicaid patients with bipolar disorder,** *Journal of Affective Disorders* (2007).

pre-marketing trials. In addition, the Zonegran® label provides a separate section on OVERDOSE, describing as little as 3 patients who ingested an overdose in an attempt to commit suicide.

290. Another antiepileptic drug with enhanced suicide warnings is Keppra (levitiracetam, approved December 1999) which compares the percentage of patients attempting suicide while taking placebo (0%) versus those taking Keppra (0.5%). The labeling, which was updated from the original label approved December 1999, also notes a completed suicide. Moreover, the Keppra label specifically discusses suicide events and suicidal behavior in the *Postmarketing Experience* section. The labels for Zonegran and Keppra demonstrate a reasonable approach to informing patients and prescribers about the risks of suicidal behavior associated with these drugs. Pfizer Defendants should have taken a similar approach with gabapentin, especially given the drug's controlling share of the marketplace and the increasing numbers of suicide attempts observed in clinical trials, the Spontaneous Reporting System and in the Pfizer Defendants' internal database.

291. The labeling for a number of other pharmaceutical products also contain enhanced warnings related to suicidal behaviors observed following their launches. These include products indicated to treat acne (Accutane), panic disorder (Prozac) and depression (Prozac, Wellbutrin, Remeron, Effexor). In many cases, these enhanced warnings were the result of postmarketing reports received following approval of the drug. This includes antiepileptic drugs that possess a mechanism of action similar to that of gabapentin.

Failure to Provide Mechanism of Action Language Regarding Brain Neurotransmitters

292. Pfizer Defendants failed to appropriately address or pursue language in the product labeling, or otherwise inform healthcare providers or patients, regarding Neurontin's mechanism of action: Neurontin reduces the release of monoamine neurotransmitters in the brain (e.g., serotonin, norepinephrine), an action that is implicated in the pathophysiology of clinical depression and suicidal behavior.[136]

293. Pfizer Defendants acknowledge the "need to define the mechanism of action of gabapentin . . . so that it can be presented in product labeling in a form that is understandable for the prescribing physician. The same information will be very useful for business managers, product Marketing, etc."[137] With knowledge that Neurontin would be used for off-label indications, attention should have been placed on informing prescribers of Neurontin's capacity to reduce the release of monoamine neurotransmitters and consequently contribute to mood and behavioral disturbances.

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[136]Pfizer Defendants have also known that Neurontin (Gabapentin), in human studies, has significantly increased the brain tissue concentrations of GABA, as demonstrated with NMR spectroscopy where the spectroscopy was "used to measure whole-brain concentrations of GABA after oral administration of gabapentin to human patients with epilepsy." *See* RR-REG 740-03550 (p.35). Increased GABA has been associated with mood and behavioral disturbances; this, too, is an action about which Pfizer Defendants failed to reasonably warn healthcare professionals and patients.

[137] *See* Pfizer_CTaylor_0012843, entitled, "Gabapentin Mechanism Work Group – Team Charter (*Draft*), September 5, 2000.

294. Pfizer Defendants have known since at least the 1980s --- since the pre-clinical, pre-FDA approval stages of Neurontin for its original epilepsy indication --- that its mechanism of action included the reduction of monamine neurotransmitters in the brain. Pfizer Defendants' documents provided for review reflect that such knowledge has been consistently recognized by Defendants throughout the development and marketing of Neurontin and up to the present time.[138]

295. In 1984, Pfizer Defendants' Research Report No. 4192-0166 (May 1984) stated the following:

> Title of Investigation: Gabapentin attenuates the release of noradrenaline and serotonin but not acetylcholine from brain slices. Abstract: In previous investigations gabapentin inhibited the release of dopamine from rabbit brain caudate nucleus slices in a similar manner as GABA and baclofen….Thus, gabapentin impaired the release of biogenic amines in a similar manner as has been reported for GABA and baclofen.[139]

296. Pfizer Defendants' research from the periods covering 1981 through 2001, as reflected in Defendants' Research Reports, reflects an acknowledgement as to the reduction of monoamine neurotransmitters. For example, Defendants' Research Report 740-03550, entitled, Summary of Preclinical Pharmacological Studies with Gabapentin (CI-0945, PD 0087842-0000) In Vitro and in Laboratory Animals, states the following:

> Gabapentin was examined for effects on the release of radiolabeled monoamine neurotransmitters from rat neocortical or striatal tissue slices in vitro. If neocortical slices were superfused with gabapentin for 15 minutes prior to application of elevated potassium ions for 120 seconds, the release of [^{3}H]norepinephrine was reduced up to 40% in comparison to the same experiment with addition of drug vehicle…. These results suggests that the inhibition of neurotransmitter release by gabapentin may occur by a reduction in depolarization-induced entry of calcium ions.[140]

297. In addition to the application of elevated potassium ions, Pfizer Defendants' research included the electrical stimulation of brain slices and specifically acknowledge that the effects of gabapentin upon monoamine neurotransmitter release could contribute to effects in behavior:

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[138] "In actions that do not appear to relate to changes in GABA systems, gabapentin binds to an auxiliary protein of voltage-gated calcium channels, the alpha-2-delta protein. Apparently in response to this binding, gabapentin reduces the release of noradrenaline, dopamine and (in trigeminal nucleus slices), the release of glutamate. The effects of gabapentin on neurotransmitter release appear to require sustained depolarization or modulation of synapses by pro-allodynic compounds like substance P or CGRP…..Therefore, it appears likely that gabapentin alters synaptic action in a way that is specific for prolonged depolarization or abnormally elevated neurotransmitter release, with relatively little effect on physiologic synaptic transmission." Pfizer_CTaylor_0001913 at 1927 (*Draft* - Antiepileptic Drugs for Treatment of Neuropathic Pain, Charles Taylor, Ph.D., Pfizer Global Research & Development

[139] *See* IND_28454_SUB_004_0101; *see* Research Report 4192-0166.

[140] *See* RR-REG 740-03550 (p.39).

> The electrical stimulation of brain slices (3 Hz stimulation for 30 seconds) also causes release of [^{3}H]norepinephrine that is reduced by gabapentin or pregabalin, but the inhibition is less pronounced (maximum of 20% inhibition). The release of [^{3}H]dopamine from rat striatal slices also was reduced significantly by gabapentin. It is possible that these effects of gabapentin on monamine neurotransmitter release contribute to their effects in anxiety and other mood disorders, but this remains to be clearly established.[141]

298. Whether the decrease of neurotransmitter release is precipitated by electrical stimulation, potassium application, or other artificial means, this hyperexcited state equates to the presence of an enhanced or excessive state of neurotransmitter release, and this is the case where individuals suffer from anxiety, as recognized by Pfizer Defendants: "And we think … that that kind of enhanced release of neurotransmitter is relevant for the pathophysiology of pain, epilepsy, and anxiety".[142] Reducing the release of neurotransmitters where there are hyperexcited cells is analogous to reducing the release of neurotransmitters where an individual suffers from an underlying disease (e.g., a disease that includes hyperexcited cells). Pfizer Defendants' witness, Charlie Taylor, Ph.D., who testified as to Neurontin's mechanism of action, stated the following in this regard:

> "Q. And if those cells are hyperexcited, the neurons in the brain, would you expect to see an impact of Neurontin on those cells that relates to the release of biogenic amines? A. I think that is a strong possibility, but I think that it remains to be tested in animal – I mean, in humans, because we don't have any data that addresses that in human beings. So that's what I would expect, but I could always be surprised."[143]
>
> ….
>
> "Q. Well, does depression have hyperexcited neuronal activity, as you described? A. I'm certain that in a depressed brain, if you studied carefully enough, **you would find regions where there is hyperexcitability.** You would probably also find regions, and I know that this is the case, there are regions that have decreased excitability."[144]
>
> ….
>
> "Q. And the human brain, when it's subject to stress, some areas may have hyperexcited neuronal activity, correct? A. Some might, but under normal resting conditions, some brains, some brain regions might have unusually elevated levels of activity."[145]

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[141] *See* RR-REG 740-03550 (p.40).
[142] Deposition of Charlie Taylor, June 4, 2007 at p.292.
[143] Deposition of Charlie Taylor, June 4, 2007, at p.321.
[144] Deposition of Charlie Taylor, June 4, 2007, at p.82 (emphasis added).
[145] Deposition of Charlie Taylor, June 4, 2007, at p.82-83.

> "Q. … If somebody is suffering from chronic pain, would you expect within their central nervous system, there would be some hyperexcited neurons? A. I think so. But, as I said, there would probably, undoubtedly be other neurons that have reduced activity."
>
> "A. Under almost any behavioral state you can name, be it depression, or pain, or anxiety, or thinking, or remembering, brain imaging studies have shown that, in general, some regions have increased activity, other regions have decreased activity. Now, whether that corresponds exactly to the hyperexcited activity that I was talking about about in vitro, is a good question. I don't think that there is a simple answer to that. We think that maybe there is a connection, but we don't know that for a fact."[146]

299. Pfizer Defendants acknowledge that the "effects of gabapentin on neurotransmitter release occur at drug concentrations that are relevant for the pharmacological actions of gabapentin in animal models (*e.g.*, approximately 10 µM or 1.5 µg/mL.)"[147] Moreover, Pfizer Defendants also acknowledge that these actions are relevant in human use. Defendants' witness, Charlie Taylor, Ph.D., testified as follows in this regard: "A. …And absolutely I think, its my opinion after writing all these papers, that concentrations of the gabapentin in the ten micromolar to 100 micromolar range are relevant for clinical practice."[148]

300. Pfizer Defendants' Project Operation Plan in March 2001 recognized the reduction of neurotransmitter release as an area of major investigation: "A second major area of investigation involves effects of gabapentin and related compounds on neurotransmitter release. Gabapentin has been known to reduce monoamine neurotransmitter release for many years."[149]

301. This disclosure by Pfizer Defendants has been made outside the U.S. Since at least 1992, Pfizer Defendants' International Regulatory Affairs have included language regarding the reduction of monoamine neurotransmitters in the Neurontin Product Profile: "Gabapentin slightly reduces the release of monoamine neurotransmitters, in vitro."[150] Yet, it remains absent from the Neurontin product labeling.

302. As part of Pfizer Defendants' pursuit of a supplemental NDA for the management of neuropathic pain associated with post-herpetic neuralgia, Pfizer Defendants submitted proposed revisions to its Neurontin labeling that included the following language: "Gabapentin reduces the stimulated release of noradrenaline, dopamine, and glutamate under certain laboratory conditions. Gabapentin administration … increases the total brain content of GABA after a single dose. However, the relevance of these findings to clinical use is not yet clear."[151] Pfizer Defendants

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[146] Deposition of Charlie Taylor, June 4, 2007, at pp.86-87.
[147] *See* RR-REG 740-03550 (p.44).
[148] Deposition of Charlie Taylor, June 4, 2007, at p.327.
[149] *See* Pfizer_MDong_0000112 at 113 (emphasis added). *See* Pfizer_CTaylor_0011878 at 0011891: "It is the most realistic mechanism that gabapentin binds to $\alpha_2\delta$ subunit of voltage-dependent Ca channel, and subsequently and partially inhibits Ca influx and excitatory transmitter releases.".
[150] *See* MAA_MISC_030_0075-7.
[151] *See* NDA21397_MISC_007_0051 at 0067.

maintain that the language was struck or otherwise rejected by the FDA.[152] Consequently, such language or similar information has never been included in the package insert.

303. Pfizer Defendants produced for deposition a "labeling" witness, Dr. Lloyd Knapp, who testified about the "value" of the subject neurotransmitter language and the reality that physicians may utilize the label for both approved and off-label indications:

> "A. We thought it was informational. We thought it was useful general information, scientific-type information. Q. And for what purpose would such useful general information, science-type information be utilized, as far as Pfizer understood? A. For --- for those physicians, healthcare providers that might be interested in further details on mechanism of action that --- that they might not otherwise be aware of from peer-reviewed public ---- or publicly available publications, literature
>
> ….
>
> Q. Are you saying that physicians would look to your label, which is meant to inform someone on approved indications, to --- because of an interest in gaining information about potential off-label uses? A. I really can't comment on what physicians may or may not do. However, you know, as a healthcare provider myself, and if there were a suggested use of a medication for which it was not approved, I would absolutely go to the label and I would look up general information that would be there that might be of interest."[153]

304. Pfizer Defendants' witness, Charlie Taylor, Ph.D., was deposed on June 4, 2007, and discussed, among other issues, the mechanism of action of Neurontin and facts related to language regarding mechanism of action being included in the Neurontin product labeling. Dr. Taylor responded to inquiries regarding the lack of language in the Neurontin product labeling as it pertained to mechanism of action and the reduced release of neurotransmitters. There was no evidence that FDA removed the language for any substantive reason; witness Taylor's only recollection is that FDA struck the language for the sake of brevity.[154] Not only should Pfizer Defendants have

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[152] *See* Deposition of Pfizer Defendants' witness Charlie Taylor, Ph.D., June 4, 2007 at pp.210-211: "Q. Have you ever attempted to do that with Neurontin or gabapentin, reach out to the FDA to revise the label? A. Well, when we filed for the post-herpetic neuralgia indication, in about 2001, there were some realized --- there was some revised wording around mechanism of action. That was submitted at the time of this submission for post-herpetic neuralgia."

[153] *See* Deposition of Pfizer Defendants' witness, Lloyd Knapp, June 27, 2007 at pp. 447- 448; *see also* Deposition of Lloyd Knapp, June 27, 2007 at p. 505: "[A]nd all of the information is summarized and that information is general useful, even for uses outside of the approved indications."

[154] *See* Deposition of Pfizer Defendants' witness Charlie Taylor, Ph.D., June 4, 2007 at pp.216-220: "Q. Do you understand that to be in the label? A. I don't think that that's in the current label, but I know that this wording at one time actually was proposed. Q. Who proposed it? A. Well, I was part of the group that proposed it, and it was a group decision what language to put in the proposed labeling that went to FDA . . . . And, you know, we had a whole bunch of competing goals, really, in coming up with the final label wording. We wanted to include as much useful information as possible that could potentially be of use to a prescriber, and we also wanted to meet the expectations of the Agency, of the Food and Drug Administration. And, you know, I have to be very honest with you, I don't recall why not all of these

continued to negotiate for the inclusion of this language as it pertained to approved indications, surely Pfizer Defendants should have sought to have this or similar language regarding the reduction of neurotransmitter release included in light of the known psychiatric and chronic pain population of patients that were susceptible to mood and behavioral disturbances with the use of Neurontin.[155]

305. The reviewed documents reflect that Pfizer Defendants wanted to expedite the approval process in light of FDA reviewer Dr. Cynthia McCormick "leaving the country for several weeks", and Pfizer Defendants were "pleased with the FDA's initial reaction and response to [their] submission"; Pfizer Defendants accepted as "OK" the FDA's revisions regarding mechanism of action.[156]

306. Pfizer Defendants' witness, Lloyd Knapp, who was produced as a "labeling" witness, testified with respect to the mechanism of action section as follows: "Just in terms of the Mechanism of Action section in general, rather than specific substance that was in there, Pfizer made proposals for additional language to be included in that Mechanism of Action section. It was removed by FDA, and I believe that at the time we did not further discuss that with FDA."[157]

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words are in the current labeling, but I suspect that was because it was just becoming a big long, and the agency actually struck some of our proposed wording, and made it simpler and shorter. Q. Do you know that with certainty? A. No. I don't know that with certainty because it was a while ago, and as I think I already mentioned, there were several versions of this label. Obviously, this is an important issue and I don't want to misstate the facts, but I do know that this wording was proposed and, I do know that it was later taken out. . . . Q. And if you proposed those words, you thought they were material and important? A. Well, as I said before, views of how something works and anything that is really a scientific investigation change over time…. But at the time, this was sort of the consensus of what we thought was relevant and of use to prescribers…..Q. If the FDA said those words should come out, would there be some documentation to that effect? Is it a phone call or is there a paper trail that would say that it's the FDA who wanted to take it out? A. . . . And my recollection, which I am not 100 percent confident about, but my recollection is FDA struck the wording and we didn't think that it was an important enough issue to prolong the whole label negotiation about to fight it, essentially…. And this mechanism of action part of the label is not a central, not of central importance. Its useful, but its not of central importance to prescribing physicians.

[155] *See* Deposition of Charlie Taylor, Ph.D., June 4, 2007 at pp.224-226: "Q. The comments that you had regarding mechanism of action in the label, are they restricted to your understanding as to how it is used for the approved indications? A. Well, I think that that is ---- again, a little bit of a difficult question to answer, because the mechanism of action of a drug is usually not, you know, a drug binds to receptors in the brain, so the receptors in the brain is same regardless of what indication is approved. And the mechanism of action wording that is in our gabapentin label is not really specific to indication, but, of course, it is the approved labeling only for post-herpetic neuralgia and epilepsy. So, for other indications that are not in the label, presumably the mechanism of action description is adequate, but it's not really designed to address other potential indications of the drug, only really to address the approved indications…..But for any conceivable indication would this mechanism description be adequate? I don't know. I mean that is a pretty broad area."

[156] *See* Pfizer_AGarrity_0002266. The exhibit states in part, "MOA (p.3). Changes OK . . . Deletion of second paragraph OK." Additionally, Pfizer Defendants' motivation not to pursue appropriate language may have been driven by a strategic effort to protect a "trade secret" as to Neurontin's mechanism of action. *See* Pfizer_CTaylor_0017230 where Pfizer Defendants' witness Charlie Taylor's email (May 23, 2002) states as follows: "I find it curious that LaMattina would suggest to go forward with alpha2-delta as a mechanism of action, when in our strategic view a couple of months ago, the sentiment was to keep much of our supporting data around alpha2-delta as a trade secret. We simply can't do both…"

[157] *See* Deposition of Lloyd Knapp, June 27, 2007 at pp.442-443. Witness Knapp did not provide any further testimony revealing that the subject mechanism of action language regarding neurotransmitter

307. Pfizer Defendants' position at the time was that they could "submit a labeling supplement at any time with the information when we are ready" and reasoned that FDA "seems eager to close this and letting it linger there always opens up possibilities for making changes that are not in our favor. I would suggest we then gather the rationale for the [mechanism of action] MOA and any other minor points and attempt to add those modifications at a latter date."[158] Nevertheless, Pfizer Defendants have never sought to revise or otherwise supplement the Neurontin product labeling, provide Dear Healthcare Provider letters, or undertake an educational campaign to inform the public or prescribers as to Neurontin's mechanism of action which reduces the release of neurotransmitters. This information would be important and relied upon by prescribers as part of their risk/benefit analysis when prescribing Neurontin, particularly for off-label, psychiatric uses.[159]

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release was struck for any substantive reason: "Q. And what documents, if any, serve as the basis for your understanding that the proposed language was stricken or struck? A. Original --- original proposed label regarding the neuropathic pain/PHN submission, feedback from the FDA which shows the deletion of those sections, and then ultimate final label that was agreed. Q. Okay. When you say "feedback", other than the language being struck with a black line --- A. Correct. Q. ---was there any other feedback from the FDA? A. I don't recall any specific feedback other than the fact that they requested it to be removed." Deposition of Lloyd Knapp, June 27, 2007 at pp. 443-444.

[158] *See* Pfizer_CTaylor_0017228.

[159] Deposition transcripts of Neurontin prescribers who have been deposed during the pendency of the litigation were reviewed. Pertinent testimony reflecting the importance of mechanism of action language, particularly regarding the reduced release of neurotransmitters has been elicited. *See* Deposition of Richard R. Burris,MD, July 18, 2007 (Roberson v. Pfizer, et al., p. 113-115) wherein he testified as follows: "Q. Is a reduction in serotonin in the brain of any clinical concern with regard to people who are being treated for depression? A. Yes. Generally speaking, if you decrease serotonin effect on the brain the depression symptoms will increase.". … Q. If Warner-Lambert or Pfizer or Parke-Davis, for that matter, had been in possession of such information, that information you would have wanted to have when you were treating Tommy Robertson? A. If it was confirmed I would want to know that so I could adjust medication dosages." *See also* Deposition of William Crotwell, III, MD, May 1, 2007 (Owens v. Pfizer, et. al. at pp. 58-60): "Q. Did you --- What significance, if any, would you have attached back then when you were prescribing Neurontin to Mr. Owens if the evidence in this case is that Neurontin, through its mechanism of action, can reduce the release of production of serotonin in the brain? A. Again, it would depend on his history, the psychiatric history. If a person is --- If they're on medications like that, then I think I would have probably questions using it. But again, I didn't have that. . . . . Q. Doctor, going back to the line of questioning about the reduction of neurotransmitter release, in general, would --- if it was given to you in understandable terms, would you want to know whether Neurontin had the capacity to reduce the release of excitatory neurotransmitters as part of your risk/benefit approach in determining whether to prescribe Neurontin in the first place? A. In general, yes, it would be." *See also* Deposition of Thomas Maltese, M.D., May 22, 2007 (Vercillo v. Pfizer, et. al., at p.172) (referencing exhibit 11; Pfizer_CTaylor_0012930 at 0012933): "Q. 'Gabapentin has been shown to reduce the stimulated release of noradrenaline, dopamine and glutamate under certain laboratory conditions. Gabapentin administration to humans has been shown to increase the total brain content of gaba after a single dose. However, the relevance of these findings to clinical use are not yet clear,' all right. Now, that was in a proposed label. Is that something that you as a psychiatrist thank would have been important to see in the label? A. Yes." *See also* Deposition of Lakshman Rasiah, M.D., May 8, 2007 (Bentley v. Pfizer, et. al, pp. 53-57): "Q. I'm going to ask you just to assume if this was evidence in the case if you attach any significance to this; that Neurontin reduces the release and production of dopamine, noradrenaline and serotonin. . . . Q. Is that important for you to know? …Q. Would you want to know that? A. Yes. …. Q. Did you know whether or not Neurontin attenuates the release of serotonin? No. Q. And did you know whether or not Neurontin attenuates or diminishes the

308. Illustrative of the importance of this mechanism of action language is its presence in Pfizer Defendants' sister drug, Lyrica® (pregabalin). Pregabalin is a compound structurally similar to gabapentin and was approved by FDA in part based upon the very research that was originally done for the benefit of gabapentin's approval by FDA. Pfizer Defendants acknowledge that it has been "established that gabapentin and pregabalin alter Ca^{2+} influx and monoamine neurotransmitter release in rat brain synaptosomes."[160]

309. Unlike gabapentin, Pfizer Defendants' pregabalin product labeling does include language reflecting the drug's mechanism of action regarding neurotransmitters as follows: "*In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function."[161]

310. Despite Pfizer Defendants' having in the market two drugs (gabapentin and pregabalin) with similar mechanisms of action and similar populations who are ingesting the drug, there is no reasonable basis why pregabalin has at least some reference to the reduction of neurotransmitters, yet gabapentin has none.[162]

311. Dr. Knapp testified that the basis for the presence of the language in the pregabalin labeling, but not in Neurontin, may simply have been based upon a change of personnel at FDA:

> "Q. And so do you have any explanation as to why the language was accepted for the Lyrica package insert but not for the Neurontin package insert? A. I don't, other than the observation that the division directors have changed in the meantime at the FDA and this could be --- this could be something of particular interest to the division director who ultimately has to approve that label. And so the division director that approved and was --- was in fact in charge of the

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release of norepinephrine [noradrenaline]? No. Q. And you would want to know all of that as relates to your treatment in the psychiatric patients? A. Ultimately clinically for its clinical value."

[160] *See* Pfizer_MDong_0000112 at 113.

[161] *See* Pregabalin (Lyrica®) U.S. Package Insert, (Revised 2005). This information is immediately preceded by a specific reference to gabapentin: "Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the $alpha_2$-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models." *See* Taylor, et. al., *Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C*, Pain 2003; Deposition of Charlie Taylor June 4, 2007, Exhibit 21: "Since inflammation and neuropathic pain cause an augmentation of stimulated neuropeptide release and because gabapentin and pregabalin are antinociceptive only in states of inflammation or neuropathy, we asked whether these drugs could block the augmentation of transmitter release produced by inflammation…. [W]e found that gabapentin and pregabalin did attenuate the stimulated release of neuropeptides from spinal cord slices taken from the side ipsilateral to inflammation. These findings suggest that gabapentin and pregabalin act on cellular mechanisms that are not active under resting conditions, but play a role in presynaptic transmitter release during pathological conditions such as inflammation."

[162] *See* Deposition of Pfizer Defendants' "labeling" witness, Dr. Lloyd Knapp at p. 492-493: "Q. The Lyrica label, in fact, has a reference to the reduction of the neurotransmitter release, right? A. I'm aware of that. . . .Q. In what --- for whatever reason it's in the Lyrica label as you --- as you referenced, what were the indications for Lyrica at the time? A. I'm just --- I'm thinking…. I believe that the indications were adjunctive therapy of epilepsy in adults, neuropathic pain that is associated with painful diabetic peripheral neuropathy, and post-herpetic neuralgia. Q. That's awfully similar to the indications for Neurontin, correct? A. Yes, it is. Q. And the mechanism of action for Lyrica or for pregabalin is awfully similar to that of neurontin, correct? A. Yes, it is."

division when the Neurontin statements were removed is different from the person who reviewed the Lyrica label."[163]

312. From a practical perspective, Pfizer Defendants had an opportunity to pursue a supplement in the Neurontin package insert because the mechanism of action language at issue could have been proposed to the same director that had favored the language in the Lyrica® labeling. Such action would have been appropriate in light of the acknowledged importance of the language by Pfizer Defendants, as well as the recognition that they could submit a labeling supplement at any time with the information when they were ready (as stated above).

Proportional Reporting Ratio (PRR) Analysis Demonstrated a Safety Signal for Suicidal Behavior

313. A pharmacovigilance calculation, employed by the pharmaceutical industry and regulatory authorities, is the Proportional Reporting Ratio (PRRs). It is used to compare different adverse events within a product or differences in adverse events between two products. This approach is fully discussed in the recognized epidemiology text book Pharmacoepidemiology, edited by Brian Strom.[164]

314. The proportion of the event of interest to the total number of reports can be compared with this same calculation for another reaction, or at another point in time or for two different drugs. The expected or null value for a PRR is 1.0 if no changes in an event have occurred. However, a signal is considered whenever the PRR exceeds one. Higher PRRs indicate greater signal strengths. Dr. Strom notes that "Examination of changes in PRRs over time may help to demonstrate how signals of adverse drug reaction can be identified as early as possible."[165]

315. PRR analysis compares the percentage of adverse event reports with a given adverse event term between multiple drugs or a background. For example, if Drug A had 1,000 reports and 40 of them were for completed suicide, this would represent 4% of the reports. If drug B had 500 reports and 10 of them were for completed suicide, this would represent 2% of the reports. The two percentages could then be compared.

316. All adverse events associated with a drug product must be known in order to calculate PRRs. If one detects a change in the proportion of a given event, compared with earlier data points, or differences between similar drugs or drugs in the same class (*i.e.* anti-epileptics), this would constitute a signal. The strength of the signal would partially dictate how the signal should be evaluated and what further action may be appropriate.

317. It is also necessary to assess all adverse events to ascertain the regulatory adequacy of a company's safety surveillance procedures for the evaluation of adverse event information and the maintenance of current product labeling. For example,

[163] *See* Deposition of Pfizer Defendants' "labeling" witness, Dr. Lloyd Knapp at pp. 493-494.
[164] Strom, B. 2000, Pharmacoepidemiology: 3rd Edition, pp 180-2
[165] Strom, B. 2000, Pharmacoepidemiology: 3rd Edition, p. 181

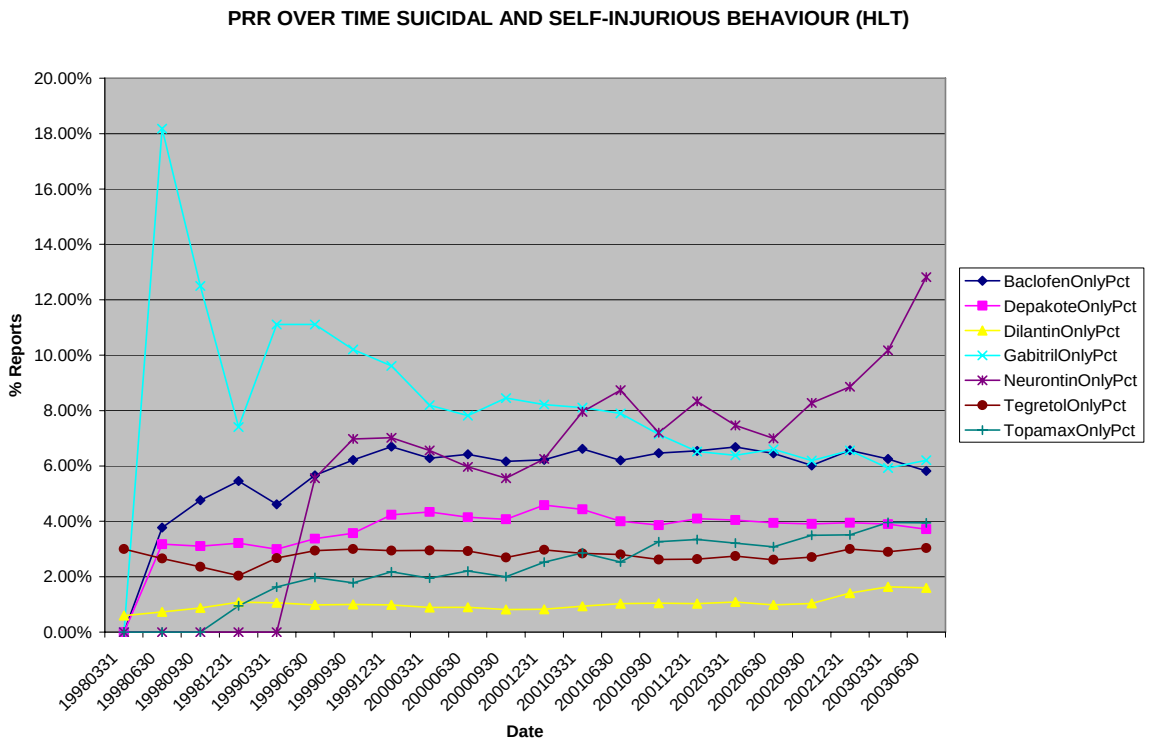
only by reviewing all the adverse events would one appreciate if the non troublesome as well as the threatening events were evenly handled with respect to labeling amplification and FDA notification.

318. In March of 2005, the FDA published Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. This document provided the FDA's non-binding recommendations on how companies should conduct pharmacovigillance activities.[166] The FDA discusses the use of several data mining tools for signal detection: one of the methods of data mining discussed by the FDA is Proportional Reporting Rate (PRR) analysis.[167] The FDA states that "[a]lthough all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products."[168]

319. With respect to Neurontin, computations for comparing Neurontin to several other drugs used to treat epilepsy or which are similar pharmacologically are provided below. For this particular analysis, publicly-available data from the FDA Adverse Event Reporting System (AERS) is utilized.

320. Included below is a chart reflecting the PRR for Suicidal and Self-Injurious Behavior. In this chart Neurontin, Gabitril, and Baclofen are at or near the top of the group. Both Neurontin and Gabitril are GABA analogues and are used heavily off-label for similar conditions. As noted previously in this report, Pfizer Defendants have noted similarities in the pharmacologic activity between Baclofen and Neurontin.

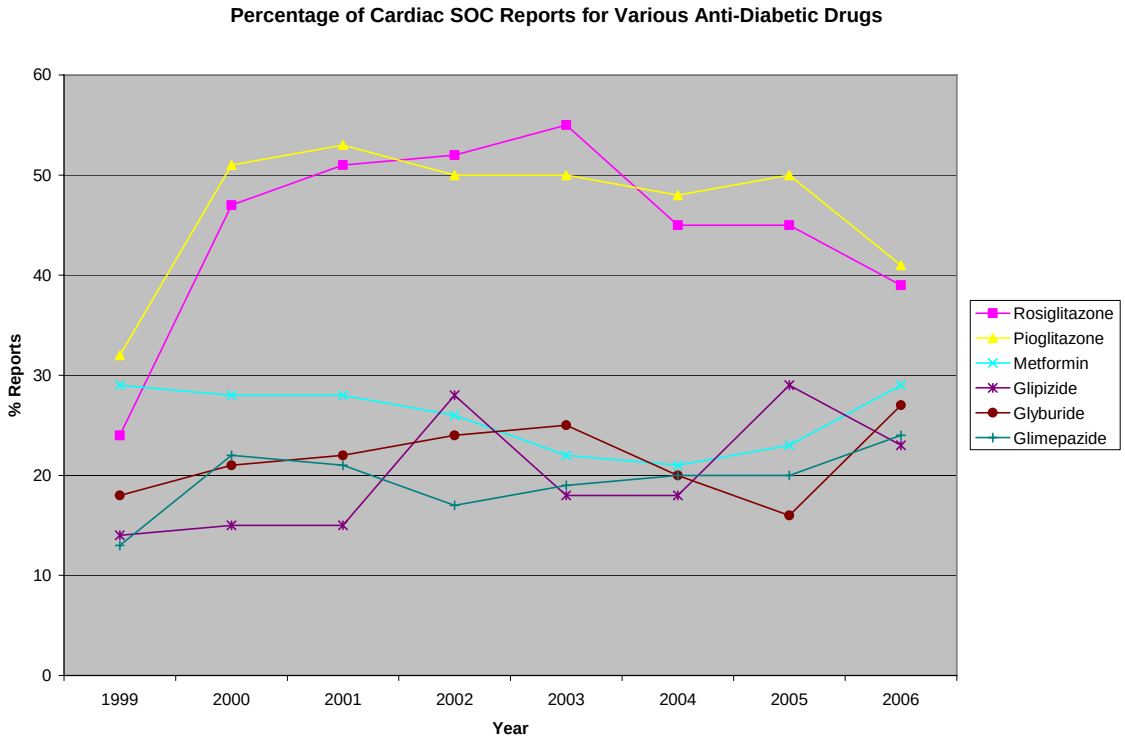
[166] *See* U.S. Dept. of Health and Human Services (FDA), Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005).
[167] *See* U.S. Dept. of Health and Human Services (FDA), Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005), at p. 9.
[168] *See* U.S. Dept. of Health and Human Services (FDA), Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005), at p. 9.



321. All three of these drugs appear to have the highest percentages of suicidal and self-injurious events over a period of years. No later than mid 2001, Pfizer Defendants had a safety signal of a possible association between Neurontin and suicidal events. Specifically, the percentage of reports reflecting serious events with Neurontin, Gabitril and Baclofen are approximately twice as much as the percentage of reports from other anti-epileptic drugs used to treat similar conditions.

322. Illustrative of PRR application by the FDA, in 2007 there were safety concerns about Avandia® (Rosiglitazone), a drug used for the treatment of diabetes. At the end of July 2007, the FDA convened an advisory committee to review the safety of the drug. In preparation of the committee meeting, the FDA prepared a briefing package.[169] The FDA performed a PRR analysis for Avandia® against other anti-diabetic drugs with respect to cardiovascular adverse events. Provided below (in chart form) is the data that FDA evaluated.

[169] *See* FDA Briefing Document, Joint Meeting Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, July 30, 2007, at p.44.



323. The FDA concluded "from 2000 to 2005 that both TZDs [Avandia and Actos] consistently showed that about 20% more of the serious outcomes are cardiac events compared to the other four hypoglycemic agents .... The finding supports an association of cardiac events with TZDs as a signal."[170] In comparing the data from the FDA for Avandia with the data reviewed for Neurontin, the data is qualitatively very similar: in both cases, the drugs of concern had percentages of reports about twice that of the other drugs. Applying the same reasoning FDA used in determining a signal with Avandia, one can similarly state that a safety signal existed for Neurontin regarding suicidal behavior.

Proposed Labeling Information

324. As previously set forth in this report, Pfizer Defendants have failed to reasonably warn healthcare professionals about the association of Neurontin with psychobiologic adverse events, including suicidal behavior. Below is language that should have been pursued by Pfizer Defendants:

a. Incidences of positive dechallenge/rechallenge events have been documented in clinical trials involving gabapentin. Dechallenge events include suicidal ideation, depression and hostility. In addition, a positive rechallenge event was documented in one patient (depression). The

[170] *See* FDA Briefing Document, Joint Meeting Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, July 30, 2007, at p.44.

temporal relationship between the tapering/discontinuation of gabapentin therapy and the resolution of the depression and suicidal ideation events in this patient suggests that gabapentin precipitated these events. As such, these dechallenge/rechallenge events demonstrate that gabapentin may be associated with adverse effects on mood and special precautions should be taken to monitor patients for any changes in their mental health status.

b. Neurontin reduces the stimulated release of noradrenaline, dopamine, and glutamate under certain laboratory conditions. Gabapentin administration increases the total brain content of GABA after a single dose. However, the relevance of these findings to clinical use is not yet clear.

c. Neurontin slightly reduces the release of excitatory neurotransmitters (*e.g.*, serotonin, norepinephrine) *in vitro*. A reduced release of excitatory neurotransmitters in the brain may contribute to depression and suicidal behavior.

d. Patients of all ages who are started on Neurontin should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

e. Depression and suicidal behavior (ideation, attempt, completed suicide) have been reported to occur in patients receiving Neurontin. Patients treated with Neurontin should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Neurontin therapy should be considered.

f. A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of Neurontin. Some of these changes may be characterized by decreased inhibition (*e.g.*, aggressiveness), depersonalization. In patients with pre-existing psychiatric conditions, worsening of depression, including suicidal thinking has been reported in association with the use of Neurontin. It can rarely be determined with certainty whether a particular instance of abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

CONCLUSIONS 2002-present

325. Despite the steady accumulation of postmarketing suicide-related events over the past several years, the Pfizer Defendants have not amplified their labeling to alert prescribers and patients to these risks.

326. The Neurontin labeling is deficient relative to those employed for other antiepileptic products and other drug products associated with self-injurious behaviors.

327. Despite the steady accumulation of biochemical and pharmacology-related information, Pfizer Defendants have not amplified the Neurontin labeling to provide information relating to its potential to elicit self-injurious events.

328. The Pfizer Defendants have not conducted the epidemiologic evaluations necessary to quantify Neurontin's adverse psychobiological and self-injurious properties and determine the most critical at-risk populations.

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